Medical Lib.

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

Vol. XXXII—No. 366] BALTIMORE, AUGUST, 1921 [Price, 50 Cents

CONTENTS

	PAGE
Chronic Meningococcus Septicæmia. A Report of Two Cases. (Illustrated.) By Hugh J. Morgan	245
Pernicious Anemia. A Clinical Study of One Hundred and Fifty Consecutive Cases with Special Reference to Gastric Anacidity. By Samuel A. Levine and William S. Ladd	254
Gland Puncture as a Diagnostic Measure. By C. G. Guthrie	266
The Present Views on Anaphylaxis. By Jules Bordet	269
Notes on New Books	276

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

CHRONIC MENINGOCOCCUS SEPTICÆMIA

A REPORT OF TWO CASES

By Hugh J. Morgan

(From the Biological Division of the Medical Clinic of The Johns Hopkins Hospital and Medical School)

During the spring and summer of 1920 there came under observation at The Johns Hopkins Hospital two examples of an unusual form of meningococcus infection, namely, chronic meningococcæmia. In both instances the organism was isolated in pure culture from the blood stream during the course of a long septic disease. The infrequency of the condition, the difficulties met with in its diagnosis, and the gratifying therapeutic results obtained by the use of specific sera, render it allowable to place these cases on record.

Meningococcæmia

Although the first authentic case of meningococcus septicæmia was reported by Gwynn in 1898, as early as 1881 Gaucher had isolated a micrococcus from the blood of a patient who later died of meningitis, and it is fairly certain that he was dealing with the same organism which Weichselbaum, six years later, called *Diplococcus intracellularis meningitidis.* Next after Gwynn's report came that of Saloman in 1902, and was followed by those of Warfield and Walker, Claude and Bloch, Rist and Paris, Martini and Rhode, Andrews, Simon, Liebermeister, Bovaird and others. French observers, more particularly, have called attention to the various clinical manifestations of this condition, most prominent among them being Netter, Claude and Bloch, Rist and Paris, Monziols and Loiseleur, Chevrel and Bourdenier, Pissavy, Richet the younger and Pignot, Portret, P.-L. Marie, Sainton and Maille, Lancelin and others.

It has been known, then, for many years that a meningococcus infection may give rise to a general septicæmia. Nevertheless, the overwhelming predominance of meningitic manifestations in instances of meningococcus infection has obscured this fact rather naturally, and one is apt to associate the organism only with cerebrospinal fever. But that it may cause lesions elsewhere, independent of, or associated with, a meningitis, has long been known.

Josia (cited by Portret) and Gwynn (in 1898) were the first to isolate the meningococcus from suppurating joints in cases of cerebrospinal meningitis. Canult described pericardial lesions, and Warfield and Walker, and Claude and Bloch observed endocardial lesions, caused by the same organism, in 1900 and 1903, respectively. Jacobitz, in 1905, reported a case of meningococcus pneumonia, followed in a few days by a meningococcus meningitis. Achard and Flandrin (cited by Portret) also noted this unusual localization. Iridocyclitis caused by the meningococcus has been described (Bovaird), as well as cerebral abscess (Manziols and Loiseleur).

When one considers that the lesions enumerated above occur in cases associated with, or independent of, cerebrospinal meningitis, he is forced to the assumption that invasion of the blood stream is not an uncommon occurrence in meningococcus

infections, and that these lesions are metastatic. Moreover, the observation of Herrick in this country, that fully 50 per cent of his cases of cerebrospinal meningitis clinically were preceded by a meningococcæmia, lends weight to this opinion which had been strongly insisted upon by Elser and Huntoon in 1909. Of this type of meningococcus infection (*i. e.*, meningococcus septicæmia) our present cases afford examples, and in order that their relative place among the meningococcus bacteræmias may be defined, a clinical classification of meningococcæmia, based on reported cases, will be given:

A. *Fulminating Meningococcus Septicæmia.*—This form represents an overwhelming infection, characterized by an abrupt onset with chill, headache, prostration, a purpuric skin eruption, a high or subnormal temperature, with collapse and death usually within 24 hours. The diagnosis is made only at autopsy (cultures) or by blood cultures taken before death from a vein or from a purpuric spot. The fulminating cases of so-called cerebrospinal meningitis undoubtedly fall into this group, many showing at section no central nervous system lesions, and others only slight evidence of meningeal localization of the infection. A number of cases, representing this form of sepsis, in which the bacteræmia has been proven by ante-mortem blood cultures, have been reported (Andrews, Anderson, Pybus, Herrick, Worster-Draught and Kennedy, Sophian, and others).

B. *Acute Meningococcus Septicæmia.*—The majority of cases of acute cerebrospinal meningitis probably fall into this group. In such instances the organisms more or less rapidly localize in the meninges, and the blood becomes sterile. It would seem highly probable that the comparatively low percentage of positive blood cultures in cases of acute cerebrospinal meningitis is dependent entirely upon the rapidity of meningeal localization, since, as a rule, after the meningitis has definitely developed, the bacteræmia disappears. Certain it is that there are cases of meningitis which are preceded by symptoms of a severe general infection of several days' duration, and in which a meningococcæmia is proved by blood culture. Many instances of this sort have been cited in the literature (Gwynn, Netter, Pissavy, Richet the younger and Pignot; Lemierre, Portret, Sophian, Worster-Draught and Kennedy, and others) and their occurrence is not uncommon in extensive epidemics of the disease.

C. *Chronic Meningococcus Septicæmia.*—It is this infrequent form of meningococcæmia to which we wish particularly to direct attention, inasmuch as our two cases fall into this group. The case histories will be followed by a discussion of the diagnostic and therapeutic problems which arise in connection with the group.

Case I.—Name: G. W. Age: 33. Sex: Male. Race: White. Occupation: Shipyard employee. Admitted June 22, 1920. Discharged August 16, 1920.

Summary.—Onset sudden, following extraction of a tooth; chills, fever, lassitude; recurring crops of erythematous nodules; joint pains; headache; weakness and loss of weight. Symptoms persisted for 56 days without change. Blood culture positive for meningococci on the 49th day, seven days before development of signs of meningitis. Cerebrospinal meningitis. Antimeningococcus serum intravenously (110 c.c.) and intraspinously (225 c.c.). Serum sickness. Recovery.

Complaint.—"Aching and numbness in legs; lumps on legs."

Family History.—Unessential.

Past History.—His general health had been excellent. He had measles and mumps in childhood, but has had no other illnesses. His habits were exemplary.

Present Illness.—On May 22 (one month before admission) a tooth was extracted, with great difficulty, under local anæsthesia. The tooth was broken several times during the procedure and a great deal of cocaine was used. That same evening he felt hot, and "had chilly sensations up and down the spine." On the following day he felt weak, his arms and legs ached, and were stiff. Hard, red nodules, varying in size from approximately 1 to 3 mm., appeared in the skin of the extremities. These nodules were somewhat tender. After a few days they disappeared.

After May 22 the patient had "chilly sensations," lasting from five to ten minutes every night and accompanied by fever. There were no sweats. The stiffness and soreness of the muscles of the extremities continued, and crops of the subcutaneous nodules appeared at intervals of from three to five days. They would gradually disappear, to be replaced by a fresh crop of lesions. During the first week of his illness he continued to work, but increasing weakness and malaise, together with the symptoms mentioned above, forced him to stop, and he had been confined to his bed since.

From the onset the patient had been troubled with anorexia and constipation. He stated that he had lost ten pounds in weight during the month previous to admission.

Physical Examination.—The temperature was 99.2° F., the pulse 80, and the respirations were 20 per minute. The blood pressure was 85 systolic and 40 diastolic. There was evidence of some recent loss of weight, and the skin and mucous membranes showed slight pallor. Scattered mainly over the extensor surfaces of the forearms and legs, and to some extent over the flexor surfaces, were numerous red and bluish-red macular and papular skin lesions, varying in diameter from 1 mm. to 2 cm. The distribution was somewhat striking, in that the lesions were for the most part confined to the extremities, the lower extremities showing more than the upper ones. Examples of all stages of development of the lesions were present—small, slightly raised, circumscribed, erythematous spots; larger, definitely elevated, red papules which were tender; still larger, dark bluish nodules 0.5 to 2 cm. in diameter, which were moderately tender. Scattered over the skin were circumscribed, very slightly pigmented areas, which were interpreted as the sites of old lesions. There was no general glandular enlargement. The examination of the head and neck showed only a small, granulating slough at the site of the extracted tooth, and evidences of chronically infected tonsils. The eye grounds were normal. Examination of the heart and lungs was negative. The pulse was soft and a little rapid. The abdomen was entirely negative; the spleen was not enlarged to percussion. Examination of the genitalia, joints and reflexes revealed no abnormalities. The rectal examination (digital) was negative.

Laboratory Examinations.—Blood: Hæmoglobin (Sahli), 80 per cent. Leucocyte count, 12,600. Wassermann, negative. Blood culture (June 23), no pathogenic organisms. Blood culture (June 26), sterile. Urine: several examinations were entirely negative, with the exception of a faint trace of albumin on one occasion.

Course in Hospital.—During the first four days of his stay in the hospital the patient ran a high intermittent fever, and there were chills and "flushes." No sweats occurred. The eruption present on admission almost entirely faded away during this time. A new nodule was noted on the left forearm, but this disappeared in forty-eight hours. The patient complained bitterly of pains in the joints and of headache. His general appearance strongly suggested sepsis.

On June 27 the patient was without fever for over 24 hours, and felt considerably better. On the following day he had a rather sharp chill, and the temperature rose abruptly to 104.5° F. Fresh erythema-

tous nodules appeared at this time, and continued to do so every few days.

During the first two weeks of July his condition remained essentially unchanged. He continued to run an intermittent, septic type of fever, associated with either definite chills or chilly sensations. His spleen became palpable during this time. He gradually became weaker and there was some loss of weight. He slept a great deal of the time, and when awake would complain of headache and pains in his joints. No evidences of meningeal involvement were present throughout this period. On July 16 his temperature rose to 105.4° F., the pulse to 110 and the respirations to 26 per minute. He seemed definitely worse, and was much more irritable and restless. On July 17 vomiting occurred and for the first time there was some rigidity of the neck. Kernig's sign was present and there was moderate exaggeration of the deep reflexes. A lumbar puncture revealed a slightly hazy cerebrospinal fluid, under normal pressure, containing 9480 leucocytes per cubic millimeter. Of these cells 98 per cent were of the polymorphonuclear type. A few Gram-negative intracellular diplococci were seen in the smear. A blood culture taken July 10 was reported to contain meningococci of the "normal" type. There were about six colonies per cubic centimeter of blood. Forty cubic centimeters of antimeningococcus serum were given intraspinously, and 40 c.c. intravenously. Cultures of the cerebrospinal fluid taken on this date (July 17) showed the meningococcus, "normal" type; a blood culture was sterile.

July 18.—Fifty cubic centimeters of antimeningococcus serum were administered intraspinously and 70 c.c. intravenously. The patient seemed somewhat improved; he was less drowsy and complained less of headache. The cerebrospinal fluid contained no organisms demonstrable by smear or culture.

July 19.—The patient was still febrile (see chart). Antimeningococcus serum (45 c.c.) was given intraspinously. No organisms were obtained from cultures of the cerebrospinal fluid.

July 20.—Antimeningococcus serum (45 c.c.) intraspinously.

July 21.—Antimeningococcus serum (45 c.c.) intraspinously. Cultures on the 20th and 21st revealed a sterile cerebrospinal fluid, although it was still somewhat turbid. The patient showed considerable improvement. A blood culture taken on the 20th was sterile. Cultures from the nose and throat and from the site of the extracted tooth were negative for meningococci.

July 22.—The patient developed the typical urticarial rash of serum sickness. A low intermittent fever persisted. The eyegrounds showed a slight hyperemia of the discs and fulness of the veins. Some retraction of the neck, and Kernig's sign, were present. These symptoms persisted for a few days and then gradually disappeared.

July 24.—The cerebrospinal fluid was clear.

July 30.—A blood culture was sterile. Lumbar puncture resulted in the recovery of clear cerebrospinal fluid, under normal pressure, containing 14 cells per cubic millimeter; it was sterile on culture.

With the disappearance of the serum sickness the patient's general condition rapidly improved. There were no recurrences of the headaches, joint pains or skin manifestations, and he was discharged August 16 entirely well, his convalescence to be completed at his home.

CASE II.—Name: V. F. Age: 28. Sex: male. Race: white. Occupation: lawyer. Admitted, July 8, 1920. Discharged, August 25, 1920. Result: well.

Summary.—Weakness and lassitude; sore throat; slight fever; headache; general muscular pains. Physical examination negative except for chronic tonsillitis and slight oral sepsis. Intermittent fever. Slight leukocytosis with polymorphonuclear percentage increase. Development of tender subcutaneous nodules; tonsillectomy; cerebrospinal fluid contained 36 cells per c.mm. and gave a positive globulin test. On the 39th day a blood culture (6th) was positive for a meningococcus (paranormal type); specific serum treatment (intravenously—75 c.c., intraspinously—155 c.c.); serum sickness; recovery.

Complaint.—"Headaches; aches all over; fever."

Past History.—Measles and mumps in childhood and an uncomplicated case of scarlet fever at the age of eight.

For several years previous to his admission to the hospital the patient had been subject to severe daily occipital headaches. During the last two years these had gradually decreased in severity.

About ten years before admission he had a transient attack of jaundice, without symptoms suggestive of cholelithiasis or serious gall-bladder or bile-duct disease.

On admission the patient stated that his general health had been rather poor for several years; that he had to force himself to his work and tired easily, and that altogether he "did not feel up to par." However, his appetite had remained good, and he had noted no loss of weight. He smoked cigarettes in moderation. No excesses of any kind were indulged in.

Present Illness.—For three months previous to his admission the feeling of lassitude and inefficiency noted in the past history had increased. Two weeks before admission to the hospital he noted that he was losing weight and that the slightest exertion tired him. His throat was somewhat sore, and he thought that he had some fever. He felt worse in the evening, when headache became a prominent symptom. He also had slight general muscular soreness.

He entered the hospital more on account of his general run-down condition than for the relief of any specific symptoms.

Physical Examination.—The temperature was 99° F., the pulse 72 and the respirations 20 per minute. Blood pressure—105 systolic, 65 diastolic. The general nutrition was rather poor. The skin was slightly sallow, but otherwise entirely negative. The glands at the angles of the jaw were palpable; there was no general glandular enlargement. Examinations of the eyes and ears were negative. The teeth showed some slight evidence of pyorrhœa. The tonsils were large and several of the crypts contained plugs. There was a slight diffuse enlargement of the thyroid gland, but no signs of hyperthyroidism were elicited. Examination of the lungs revealed possibly a slight impairment of the percussion note over both apices, but no changes in the breath sounds were present, and there were no râles. The heart was normal in size and position and the sounds were clear. The peripheral vessels were soft. Examination of the abdomen was entirely negative. The genitalia and extremities were normal. No clubbing of the fingers or toes was present. The superficial and deep reflexes were present and normal.

Laboratory Examination.—Blood: R. B. C., 4,512,000. Hæmoglobin (Sahli), 85 per cent. Color index, 0.9. W. B. C., 10,600. Aside from slight pallor of the red cells and the leukocytosis the stained film revealed nothing abnormal.

Differential count:

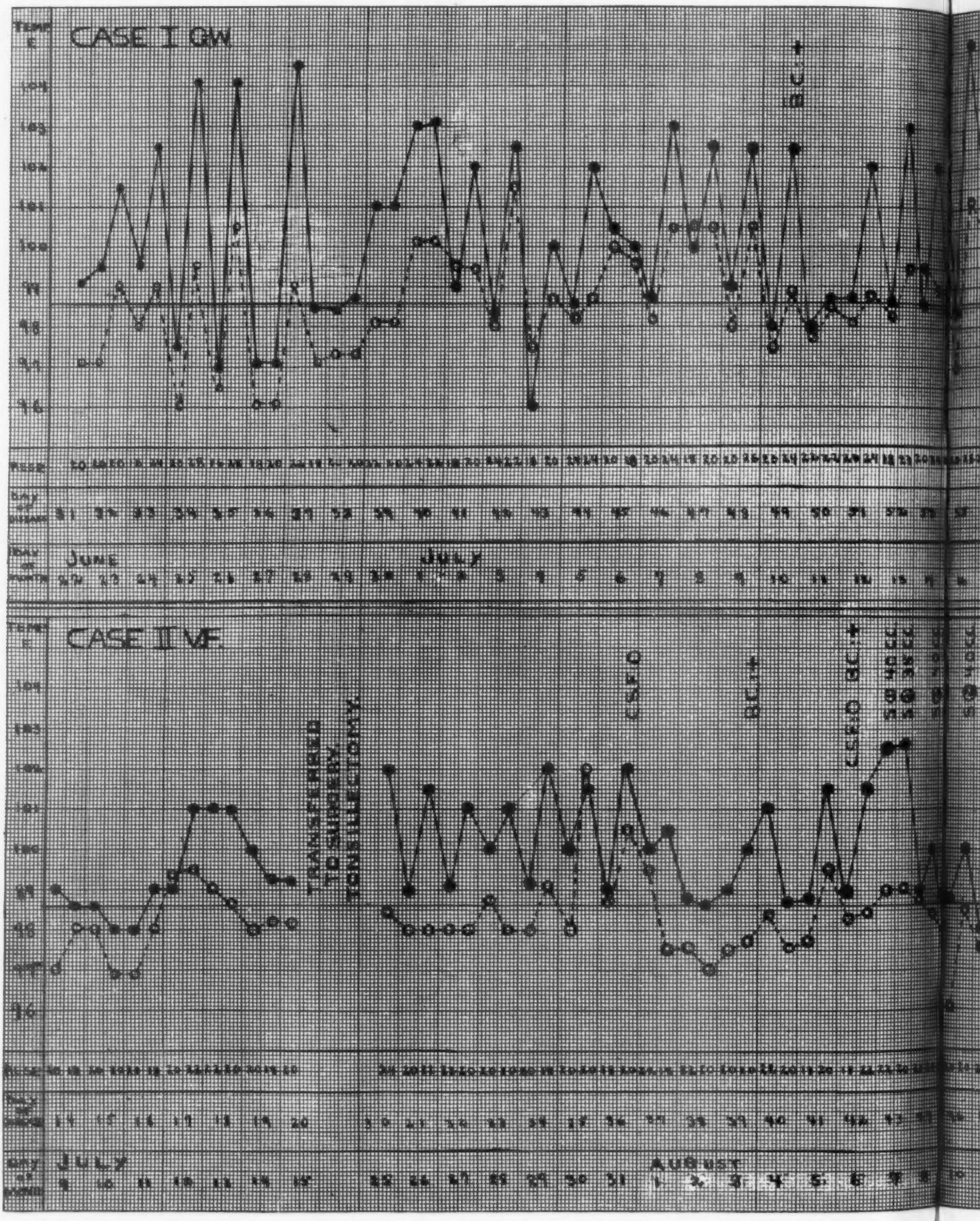
	Per cent
Pm. N.....	73.5
Pm. E.....	0.5
Pm. B.....	0.0
Large mononuclear cells.....	19.5
Small mononuclear cells.....	2.0
Transitional cells.....	4.5
	100 (200 cells counted.)

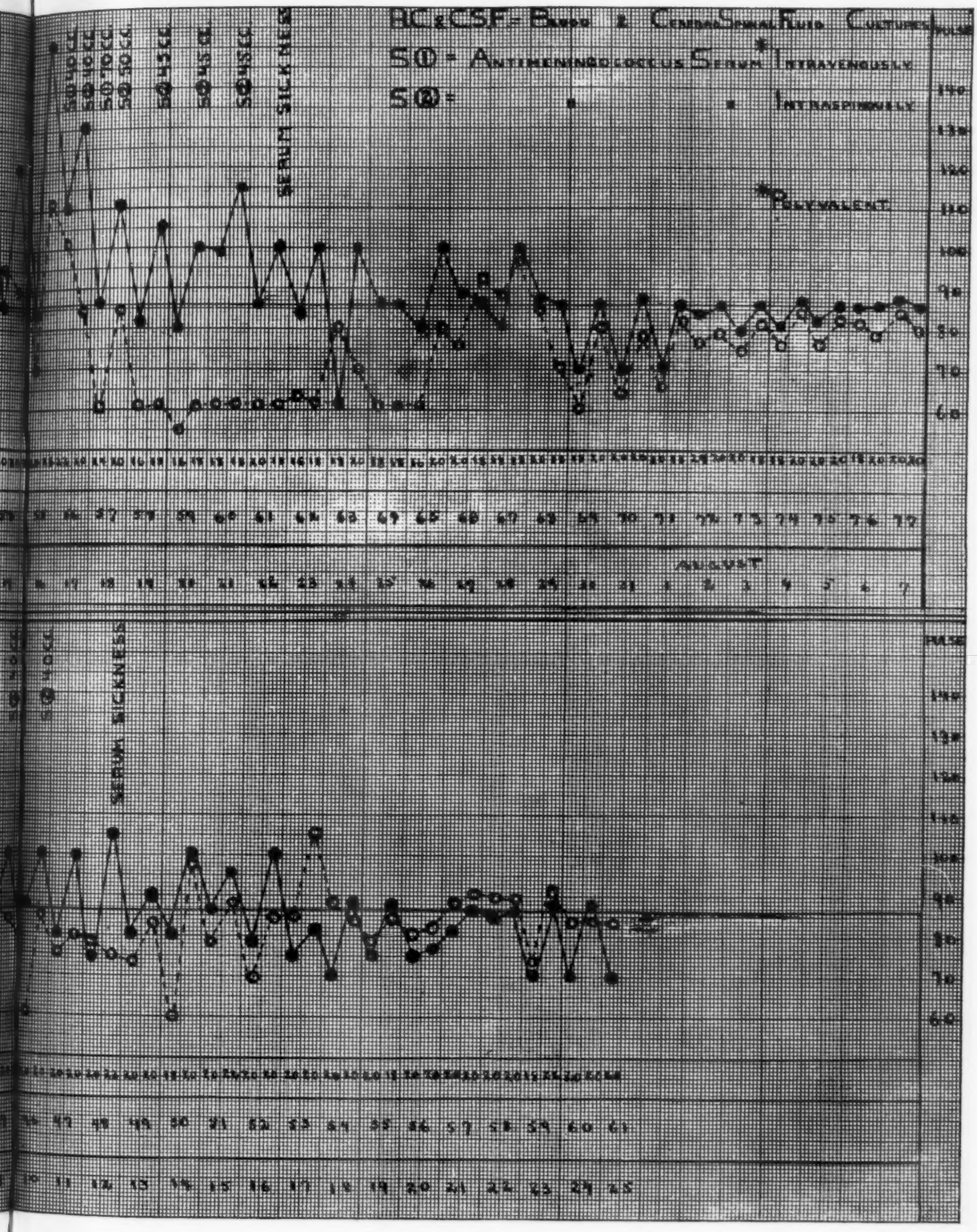
Urine: S. G., 1020; acid; albumin—trace; an occasional hyline cast. Tests for bile and blood were negative. The day after admission the trace of albumin disappeared, and no casts were found on microscopic examination.

Wassermann reaction (blood), negative.

Blood cultures made on the day of admission, and repeated two days later, remained sterile.

An x-ray plate of the chest revealed moderate fibrosis of both lung apices—probably an old tuberculous process. An examination of


CASE I GW.
CASE II VF.
TRANSFERRED TO SURGERY FOR ILEOSTOMY
JUNE
JULY
AUGUST


BC&CSF = Blood & Cerebro Spinal Fluid Cultures
SO = Antimeningococcus Serum *Intravenously
SO = " " Intraspinously
*Polyvalent
Serum Sickness
Pulse
Pneumococcus
Streptococcus
Staphylococcus
Gonococcus
Meningococcus
Day of Illness

the feces was negative. A dental consultation revealed three impacted molar teeth, and one tooth showing periapical infection.

Course in Hospital.—During the first three days of his stay in the hospital the patient was afebrile and there were no striking developments. The only complaints were of lassitude and slight headache. On the fourth day the temperature rose to 101° F. and headache and joint pains were complained of. No chills or sweats developed. A laryngologist advised the removal of the tonsils, feeling that, in the light of the negative findings elsewhere, they might explain his condition. On July 13 there appeared on the dorsum of the right hand a small nodule approximately 1 cm. in diameter, elevated and presenting a red center. It was quite tender. A similar nodule appeared simultaneously on the dorsum of the right foot. There were no petechiæ or other skin manifestations.

On July 15 the patient was transferred to the surgical service for tonsillectomy. This was performed under general anæsthesia, and the patient made an uneventful recovery from the operation.

On July 25 the patient was readmitted to the medical service. During his ten-day stay in the surgical ward there had been no improvement. Fever, pains in the joints, malaise and general weakness persisted. On this admission examinations revealed no new development other than a heavy trace of albumin in the urine. An x-ray plate of the paranasal sinuses was reported normal. Blood cultures, made on July 26 and 27, were sterile.

On July 31 lumbar puncture was performed and 10 c.c. of clear limpid fluid, under slightly increased pressure, were removed. The cell count was 30 per c.mm., and there was a positive globulin test. The colloidal gold curve was normal, and the Wassermann test negative. Cultures of this fluid and of the blood, taken on the following day, were negative. The headache was somewhat relieved by the lumbar puncture.

On August 3 a few bright red, maculopapular skin lesions were noted and another blood culture was made (the sixth since his admission to the hospital). This culture was reported, three days later, as showing a meningococcus, "paranormal" type. This report was confirmed by a second positive blood culture taken on August 6. Specific anti-meningococcus treatment (intravenous and intraspinous) was immediately instituted.

August 7.—Forty cubic centimeters of polyvalent antimeningococcus serum were given intravenously and 35 c.c. subthecally. The cerebrospinal fluid, withdrawn before the introduction of the serum into the spinal canal, was clear, contained 48 cells per c.mm., and gave a positive globulin test. The Wassermann test and colloidal gold curve were negative. The fluid was sterile.

August 8.—Forty cubic centimeters of antimeningococcus serum (polyvalent) were injected intraspinously. There was moderate headache and the temperature reached 100° F. (maximum for the day). His general condition seemed better. The cerebro-spinal fluid was sterile.

August 9.—Thirty-five cubic centimeters of antimeningococcus serum were injected intraspinously and 40 c.c. intravenously. The cell count of the fluid removed at the time of the intraspinous treatment was 315 per c.mm. It was negative on culture. There was slight stiffness of the neck, and Kernig's sign was present, but the patient had become afebrile and his general condition was distinctly improved.

August 10.—Forty cubic centimeters of antimeningococcus serum were given intraspinously. The cerebrospinal fluid cell count was 815 per c.mm.

August 11.—He was much better. Ophthalmoscopic examination was negative. On the following day serum sickness developed, associated with the typical urticarial rash, low intermittent fever, and headache. This persisted for five days.

Following the disappearance of the serum disease, the patient made a rapid recovery. The headaches, skin eruption, joint pains and malaise entirely disappeared and he began to gain in weight rapidly. On August 25 he was discharged to complete his convalescence at his home.

Discussion

Saloman, in 1902, reported the first instance of this type of meningococcus septicæmia. The history and course of the disease in his case were typical and will therefore be briefly summarized here:

A woman, 35 years old, suddenly began to have pains in her joints. The next day a chill followed by fever and malaise developed, and a skin eruption appeared. Four days later she entered the hospital complaining of her joints, and of general weakness. The temperature was 36.6° C. and rose to 39.2° C. It persisted and was septic in type. A purpuric eruption was present and the spleen was palpable. There was a trace of albumin in the urine. On the seventh day of her illness herpes labialis was noted, and a new crop of purpuric and petechial spots appeared. The following day *Diplococcus intracellularis* (*Weichselbaum*) was cultivated from her blood. Some of the skin lesions were nodular in type. After a course of almost two months' duration characterized by chills, high but remittent temperature and multiform erythematous skin eruptions, a convulsion occurred with the subsequent development of symptoms and signs of cerebrospinal meningitis. The specific organism was recovered from the cerebrospinal fluid. After a stormy course the temperature finally reached normal on the 120th day of the disease, and the patient made a good recovery.

Cases similar to the above have been reported by Netter (1903); Rist and Paris (1904); Martini and Rhodes (1905); Liebermeister (1908); Bovaird (1909); Lemierre, May and Portret (1912); Sakai; Ottinger, P.-L. Marie and Baron (1913); Bray; Sainton and Maille; Kohlisch (1915); Netter; P.-L.Marie, Zeissler and Reidel (1917); Ribière, Herbert and Bloch (1919); Sergent and Bordet (1920) and others. There is a remarkable similarity in these reports, which has led some French writers on the subject to conclude that the condition can be diagnosed at the bedside, without the help of laboratory findings. The clinical features emphasized will be hastily reviewed at this point.

The history is usually that of a disease of sudden onset, characterized by chills, fever and malaise. Drenching sweats may occur. Headache is common. There may be nausea and vomiting at the onset, though gastro-intestinal symptoms are not prominent. As the condition progresses, weakness, irritability and anorexia ensue, and the patient, if not forced to do so at the beginning, soon takes to his bed. Joint and muscle pains are common, and a multiform erythematous eruption almost invariably appears. In the latter condition the dominant finding is a raised, firm, nodular, red or bluish-red lesion varying in size from 0.25 to 2 cm. in diameter, and usually tender. These lesions appear in crops and gradually disappear, only to recur in the course of a few days.* The temperature curve varies in type though it is characteristically of a rather high but remittent or intermittent variety, with occasional days of entire freedom from fever. Netter particularly

* Renault and Cain have studied similar lesions occurring in nine cases of cerebrospinal meningitis with meningococcus septicæmia. The major changes occurred in the blood vessels and in the neighborhood of the capillaries. The presence of the meningococcus here was proven both microscopically and culturally.

called attention to the remittent type of the febrile reaction, and this has been noted by others, especially Lancelin, Bour, Sevestre and Hutinel. The chart may be very similar to that of a tertian or quartan malarial infection.

On examination, the patient presents the usual picture of a mild type of sepsis, with certain modifications. The skin manifestations, as mentioned above, are prominent, and form the most constant and characteristic clinical feature of the disease. Attention has been called by many observers, more especially by Netter, to the association of erythema nodosum with cerebrospinal meningitis and meningococcus septicæmia.

There is often a slight general glandular enlargement, although this is by no means a constant finding. The occurrence of an iridocyclitis was reported in one case.

A mild bronchitis is frequently present, though its occurrence is not so constant here as in typhoid fever, with which meningococcæmia has been confused. The heart shows nothing. It is interesting that a few cases associated with pulmonary tuberculosis have been reported. (Pissavy, Richet the younger and Pignot; Combe, Léon and Blaye; Bray.) The pulse is usually rapid in proportion to the height of the fever although a relative bradycardia may occur (suggestive of meningeal involvement). A firm spleen is frequently made out early in the course of the disease and the edge is invariably palpable below the costal margin after the affection has persisted for some time. The joints are often tender and may show a considerable limitation of motion. An actual purulent arthritis is very uncommon, although it may occur. Simple arthralgia with slight limitation of motion is the usual finding. Signs of involvement of the central nervous system are entirely absent in the premeningitic stage. As has been pointed out, however, those cases which do not receive specific antimeningococcus therapy are prone to develop a typical cerebrospinal meningitis, with the usual symptoms and signs. Examination of the blood usually reveals a well-marked leukocytosis (15,000 to 25,000), with a relative and actual polymorphonuclear increase. The latter, however, is not constant. A mononucleosis may occur (Ottinger, P.-L. Marie and Baron) and in the absence of an outspoken leukocytosis, this may lead to errors in diagnosis (typhoid fever, tuberculosis). The urine is usually concentrated, and contains a trace of albumin with an occasional hyaline or finely granular cast. Examination of the cerebrospinal fluid may be entirely negative, or may reveal a moderate pleocytosis and a positive globulin test. Cultures of the fluid are, of course, negative in the "premeningitic" stage.* As will be mentioned later, the presence of a positive globulin test and a high lymphocytosis in many of these cases, has led some observers to believe that the focus, from which the organism is disseminated into the general circulation, is situated at least in the proximity of the central nervous system. Cultures of the blood reveal the causative agent of the disease.

The most characteristic single clinical finding in the cases reported has been the painful erythematous nodules, which appear in crops, and which, on disappearing, do not leave the well-marked bluish discoloration of the skin so constant in erythema nodosum. The presence of these lesions, together with arthralgia or myalgia, is highly suggestive, when occurring in a patient running a prolonged septic course, and in whom the commoner causes of long continued, irregular or intermittent fever have been excluded.

However, a definite diagnosis of chronic meningococcus septicæmia can be made only after the presence of the organism in the circulating blood has been demonstrated by culture.†

If, during the course of a prolonged septic fever accompanied by the phenomena mentioned above, evidences of meningitis appear, one may be almost certain that a chronic meningococcæmia has been present, and that "localization" of the organisms in the meninges has occurred.

TREATMENT

Every effort should be directed toward the immediate sterilization of the blood stream before the infection has had time to become localized in the meninges, and thus give rise to an acute cerebrospinal meningitis.

Once the diagnosis is made, intensive intravenous antimeningococcus serum therapy should be started, due precautions against untoward serum reactions having been observed.

The question of subthecal treatment is an important one, and has been discussed at length by Ribierre, Herbert and Bloch in their article on this subject. According to these authors there are two definite indications for intraspinous serum therapy: (1) Evidence suggestive of meningeal localization of the organism, that is, signs of meningitis (increased irritability, rigidity of the neck, Kernig's sign, increased reflexes, an increased cell count in the cerebrospinal fluid or the recovery of the organism from the fluid). (2) Cases which do not respond promptly to treatment solely by the intravenous route.

Under the first group fall two classes of cases, (a) those with frank signs of an acute meningococcus meningitis, (b) those with only slight or inconspicuous evidence of actual meningeal

* Lumbar puncture in cases of suspected and proven meningococcus septicæmia may not be devoid of danger. It should be practised only in the presence of meningeal symptoms, or as a means of providing an additional route for the administration of serum. Weed, Wegeforth, Ayer and Felton found that release of cerebrospinal fluid during certain *artificial* septicæmias in animal experiments resulted in the meningeal localization of the organism. Wegeforth and Latham report two cases of pneumococcus septicæmia; in one of these lumbar puncture was performed on account of the presence of meningitic symptoms; in the other these symptoms were absent, but the procedure was carried out for the purpose of completing the clinical study of the case. In both instances normal spinal fluid was obtained at the initial puncture. Meningitis subsequently developed in each case.

† The medium employed (agar-agar or bouillon) should be enriched by the addition of hydrocele, ascitic or pleural fluid, approximately 1 c. c. of fluid for each 10 c. c. of medium. 0.5 per cent glucose may be added. The bouillon should be incubated for half an hour before inoculation. Blood should be drawn during the chill, or at the beginning of the daily rise of temperature, and the medium immediately inoculated, preferably at the bedside.

infection. The former should be treated as ordinary cases of cerebrospinal meningitis, the major therapy being directed to the local condition (*i. e.*, the meningitis). Here, as in the epidemic form of the disease, the usual occurrence is for the bacteræmia to disappear with the development of the meningitis. However, should the meningococcæmia persist, both intravenous and subthecal administration of the anti-serum is indicated. In the second type (b) headache, photophobia, slight muscular rigidity, a suggestive Kernig's sign and somewhat heightened reflexes may occur. The cerebrospinal fluid is clear and its pressure not greatly increased. The cell count may be high (30 per c. mm. in our case) but the cells are mainly lymphocytes. A positive globulin test may be present. The fluid, however, is sterile on culture. It is this combination of clinical and laboratory findings that has led to the assumption by some observers that the primary focus of the infection is situated at a point in close proximity to the central nervous system. They do not, however, regard these phenomena as evidence of an actual meningeal infection. Regardless of the cause, the therapeutic indications seem clear in the presence of these findings. Such patients should be treated by subthecal injections of the anti-serum, either as a curative or a prophylactic measure.

A few uncomplicated cases in the literature have responded very slowly to the intravenous treatment alone, and it is urged by members of the French school that they be treated intraspinously as well, even in the absence of any evidence of meningeal irritation. These authors base their reasoning on the belief that the focus from which the organism is disseminated into the blood stream is located near the central nervous system, and that intraspinous therapy together with intravenous therapy offers the logical approach to this focus. Although this question did not arise in the treatment of our two cases (one having developed a frank meningitis, and the other showing evidences of meningeal irritation, before specific serum therapy of any sort was instituted), no hesitancy would have been felt in resorting to the intraspinous route as an aid to the treatment of pure meningococcus septicæmia without central nervous system manifestations.

The treatment of complications of the disease other than the meningitis will not be discussed here. They are dealt with as in epidemic and sporadic cases of cerebrospinal meningitis.

Serum.—Authorities urge the immediate classification of the organism (normal, paranormal or irregular; Type I, II, III or IV of Gordon; Type A, B or C of Nicolle) in order that monovalent serum may be used. When delay occurs in determining the type, temporary treatment with a polyvalent serum may be instituted. In both of the cases here reported (one an infection with a "normal," and the other with a "paranormal" strain) the monovalent serum treatment was not feasible at the time. Satisfactory results were obtained by the use of a polyvalent anti-meningococcus serum furnished by the New York State Board of Health.

Dosage.—Daily intravenous injections of from 20 to 40 c. c. of serum are advocated. In most of the reported cases from three to five treatments sufficed. When intravenous treatment is contemplated, an equal amount may be given by this route.

Ribierre, Herbert and Bloch advocate the following procedure in the treatment of an uncomplicated case of chronic meningococcæmia: Type the causative organism immediately, and use the specific anti-serum as soon as possible. Until this is available a polyvalent serum should be employed. The treatment is begun with the daily injection of 40 c. c. of anti-meningococcus serum on one day subcutaneously and on the next intramuscularly, until five treatments have been given. If no immediate improvement results, the intravenous route should be utilized. If this fails, the serum should be given subthecally.

Vaccine Therapy.—Sergent and Provost report a case of chronic meningococcus septicæmia in which intravenous therapy (in all 100 c. c.) was without curative effect, and in which intraveneous vaccine treatment was finally employed. The patient recovered promptly. Adherents to this form of therapy, and especially Boidin, advocate also the production of an "abscess of fixation" as a definite curative measure, successful in cases in which all other forms of therapy produce no results.

In both of our cases, inasmuch as the patients were promptly cured by intravenous and intraspinous serum treatment, the other procedures recommended were not employed. From a careful review of the literature it seems that a large majority of cases respond in a similarly prompt and satisfactory manner, and that it is only the rare exception which demands other measures.

BIBLIOGRAPHY

Gaucher, E.: "Note sur le parasitisme de le méningite cérébro-spinale et sur la néphrite infectieuse qui l'accompagne." Gaz. méd. de Par., 1881, 6 s., III, 125.

Gwynn, N.: "A case of general infection by the Diplococcus intracellularis of Weichselbaum." Phila. Med. Jour., Phila., 1898, II, 1255.

Osler, W.: "The Cavendish Lecture on the Etiology and Diagnosis of Cerebrospinal Fever." Phila. Med. Jour., Phila., 1899, IV, 26.

Canult, E.: "Méningite cérébro-spinale épidémique (méningocoque)." Thèse de Paris, 1900, G. Carré et C. Naud.

Saloman, H.: "Ueber Meningokokkenseptikämie." Berl. klin. Wchnschr., Berl., 1902, XXXIX, 1045.

Claude, H., and Bloch, P.: "Sur un cas de méningite cérébro-spinale compliquée d'endo-myocardite." Compt. rend. Soc. de biol., Par., 1903, LV, 84-86.

Kutscher: Handb. der Pathogen. Mikroorgan. Kolle und Wassermann, 1903, I, 481.

Lenhartz: Spez. Path. von Nothnagel. Art. "Septische Erkrankungen," 1903.

Warfield, L., and Walker, J.: "Acute ulcerative endocarditis caused by the meningococcus (Weichselbaum)." Bull. of the Ayer Clin. Lab. of the Penna. Hosp., Phila., 1903, No. 1.

Bettencourt, A., and Franca, C.: "Ueber die Meningitis cerebro-spinalis epidemica und ihren specifischen Erreger." Ztschr. f. Hyg. u. Infectionskrankh., Leipz., 1904, XLVI, 463-516.

Rist, E., and Paris, A.: "Contribution à l'étude clinique et expérimental de la méningite cérébrospinale à diplocoque de Weichselbaum." Arch. générales de méd., Par., 1904, I, 449.

Jacobitz: "Ueber epidemische Genickstarre." Münch. med. Wochnschr., Münch., 1905, LII, 2178.

Martini and Rhode: "Ein Fall von Meningokokken Septikämie." Berl. klin. Wochnschr., Berl., 1905, XLII, 997.

Andrews, F.: "A case of acute Meningococcal Septicæmia." Lancet, Lond., 1906, I, 1172.

Gordon, M.: "Report to the Local Government Board on the micrococcus of epidemic cerebrospinal meningitis and its identification." Lond., 1907, Darling and Son.

Marchiafava, E., and Celli, A.: "Zur Geschichte der Entdeckung des Micrococcus intracellularis meningitidis." Centralbl. f. Bakt. (Orig.), 1907, XLIII, 142.

Simon: "Meningococcus septicæmia. Demonstration of the meningococcus in the blood smear." Jour. A. M. A., Chicago, 1907, XLVIII, 1938.

Liebermeister, G.: "Ueber meningokokkensepsis." Münch. med. Wochenschr., 1908, LV, 1978.

Barbier and Vaucher: "Huit cas de méningite cérébrospinale dont cinq traités par le sérum de Dopter." Bull. et mém. de la Soc. méd. des hôp. de Par., 1909, XXVII, 3 s., 871.

Bovaird, D.: "Meningococcus septicæmia with sterile cerebrospinal fluid; Iridocyclitis; Flexner's serum; Recovery." Arch. of Internal Med., Chicago, 1909, III, 267.

Achard and Flandrin: "Méningite fulm. et méningée." XI. Congrès de Médécine, Paris, 1910 (cited by Portret).

Chevrel and Bourdiniere: "Septicémie méningococcique essentielle à caractères de fièvre intermittente. Traitement par le sérum antiméningococcique." Bull. et mém. de la Soc. méd. des hôp. de Par., 1910, XX, s. 3, 165.

Monziols and Loiseleur: "Deux cas de méningococcémie sans méningite cerebrospinale." *Ibid.*, 1910, XXIX, s. 3, 155.

———: "Septicémie méningococcique avec érythème noueux primitif, compliquée secondairement de méningite cérébro-spinale." *Ibid.*, 773.

———: "Méningite cérébrospinale et abscès cérébral à méningocoque." Gaz. hôp., 1910, No. 134, 1828 (cited by Portret).

Jochmann, G.: "Septische Erkrankungen." Handb. d. Inner. Med., Mohr und Staehelin, 1911, I, 707.

Pissavy, Richet fils et Pignot: "Typhose méningococcique." Bull. et mém. de la Soc. méd. d. hôp. de Par., 1911, XXXII, s. 3, 576.

Barral, Coulomb and Couton: "Un cas de septicémie paraméningococcique traitée par le sérum antiparaméningococcique." *Ibid.*, 1912, XXXIII, s. 3, 829.

Lemierre, May and Portret: "Méningococcémie avec localization méningée tardive." Gaz. d. hôp., Par., 1912, LXXXV, 1103.

Portret, S.: "Les méningococcémies (septicémies méningococciques)." Thèse de Par., 1912, No. 41, H. Panlin et Cie.

Oettinger, P.-L. Marie, and Baron: "Un noveau cas de septicémie à paraméningocoque avec épisode meningé à repétition." Bull. et mém. de la Soc. méd. de hôp. de Par., 1913, s. 3, XXXV, 935.

Sakai, S.: "Meningokokken septikaemie ohne Meningitis." Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1913, X, 335, 5 pl.

Sophian, A.: "Epidemic cerebrospinal Meningitis." St. Louis, 1913, C. V. Mosby and Co.

Baur, J., Sevestre, J., and Hutinel, J.: "Meningococcémie benigne à type de fièvre intermittente consécutive à une méningite cérébrospinale; guérison. Ann. de méd., Par., 1914-15, II, 589-594.

Netter, A.: "Les méningites cérébrospinales frustes." Monde médical, Par., 1914, No. 508, 129.

Bray, H.: "Chronic meningococcus septicæmia associated with pulmonary tuberculosis." Arch. Int. Med., Chicago, 1915, XVI, 487.

Köhlisch: "Bakteriologische Befunde bei einem Fall von Meningokokkensepsis; gibt es eine Mutation bei Meningokokken?" Ztschr. f. Hyg. u. Infektionskr., Leipz., 1915, LXXX, 404.

Lafosse, P.: "Manifestations articulaires dans la méningite cérébrospinale." Bull. et mém. de la Soc. méd. d. hôp. de Par., 1915, s. 3, XXXIX, 299.

Sainton, P., and Bosquet, J.: "Les types cliniques de la septicémie méningococcique." Rev. gén. de clin. et de thérap., Par., 1915, XXIX, 689. *Also:* Med. Press and Circ., Lond., 1917, n. s., CIII, 7.

Sainton, P., and Maille, J.: "Méningococcémie à forme attenuée et erythème rubéoliforme." Bull. et mém. de la Soc. méd. d. hôp. de Par., 1915, s. 3, XXXIX, 296.

———: "Eruption rubéolique et septicémie méningococcique." *Ibid.*, 375.

Svestha, V.: "Meningokokkensepsis." Wien. klin. Wchnschr., Wien, 1915, XXVIII, 1319.

Bonnel and Joltrain: "Méningites cérébrospinales latentes." Bull. et mém. de la Soc. méd. d. hôp. de Par., Par., 1916, XXXX, s. 3, 75.

Dal Canton, T.: "Due casi de setticemia meningicoccica, curati con iniezioni endovenose di siero antimeningococcico." Policlin., Roma, 1916, XXIII, 821.

Elliott, W.: "A case of meningococcal infection without involvement of the cerebrospinal system." Lancet, Lond., 1916, II, 1010.

Gordon, M., Hine, T., and Flack, M.: "An experimental study of the cultural requirements of the meningococcus." Brit. Med. Jour., Lond., 1916, II, 678.

Anderson, W., McNee, J. (*et al.*): "Cases of meningococcus septicæmia." Jour. R. A. M. C., Lond., 1917, XXIX, 463.

Flexner, S.: "Mode of infection, means of prevention and specific treatment of epidemic meningitis." Jour. Am. Med. Assn., Chicago, 1917, LXIX, 639.

Gordon, M.: "Bacterial studies in the pathology and preventive control of cerebrospinal fever among the forces during 1915 and 1916. II. The definition of the meningococcus." Med. Research Com., Nat. Health Insurance, Special Rep. Series, No. 3, 1917, 10.

Lancelin, R.: "Méningococcémie à caractères de fièvre intermittente au déclin d'une méningite cérébro-spinale grave avec coma prolongé, purpura généralisé, etc." Bull. et mém. de la Soc. méd. d. hôp. de Par., Par., 1917, s. 3, XLI, 1011.

Marie, P.-L.: "Deux cas de septicémie prolongée à type pseudopalustre avec épisode méningé tardif dû à des germes voisins du méningocoque; guérison par le sérum polyvalent antiméningococcique." *Ibid.*, 259.

Morpurgo, B., and Ferrio, L.: "Setticemia meningococcica senza fenomeni de meningite." Gior. d. r. accad. de med. di Torino, 1917, s. 4, XXIII, 386.

Netter, A.: "Fièvre intermittente par septicémie méningococcique." Bull. et mém. de la Soc. méd. d. hôp. de Par., Par., 1917, s. 3, XLI, 1018. *Also:* Brit. J. Child. Dis., Lond., 1918, XV, 1.

Pybus, F.: "A case of fulminating meningococcus septicæmia." Lancet, Lond., 1917, I, 803.

Tulloch, W.: "On the differentiation by means of the absorption or agglutinin test for types of meningococci, etc." Jour. R. A. M. C., Lond., 1917, XXIX, 66.

Zeissler, J., and Riedel, F.: "Zwei Fälle von Meningokokkensepsis ohne meningitis und ihre Diagnose." Deutsche med. Wchnschr., Leipz., 1917, XLIII, 258.

Herrick, W.: "The intravenous serum treatment of epidemic cerebrospinal meningitis." Arch. Int. Med., Chicago, 1918, XXI, 541.

Ribierre, P., Herbert, P., and Bloch, M.: "Meningococcémie sans épisode méningé ou à épisode meningé tardif." Essai de pathogénie. Traitement." Ann. de méd., Par., 1919, VI, 341.

Weed, L., Wegeforth, P., and Ayer, J.: "The Production of Meningitis by Release of Cerebro-spinal Fluid During an Experimental Septicemia." Jour. Am. Med. Assn., Chicago, 1919, LXXII, 190.

Wegeforth, P., and Latham, J.: "Lumbar Puncture as a Factor in the Causation of Meningitis." Am. Jour. Med. Sci., Phila., 1919, CLVIII, 183.

Worster-Drought, C., and Kennedy, A.: "Cerebrospinal Fever." London, 1919, A. and C. Block, Ltd.

Bloch, M., and Herbert, P.: "Fièvre pseudo-palustre gonococcémique. Guérison par auto-vaccinothérapie." Bull. et mém. de la Soc. méd. d. hôp. de Par., Par., 1920, 3 s., XLIV, 277.

Herrick, W.: "Meningococcus Sepsis." System of Medicine, Nelson, 1920, I, 123.

Renoult, J., and Cain, A.: "Preuves histologiques et bactériologiques de l'origine septicémique de purpura de la méningite cérébrospinale." Ann. de méd., Par., 1920, VII, 114.

Rolleston, H., and Andrews, F.: "Cerebrospinal Fever." System of Medicine, Nelson, 1920, II, 54.

Sergent, E., Provost, P., and Bordet, F.: "Septicémie à méningocoque C sans réaction meningée. Guérison par vaccinothérapie intraveineuse." Bull. et mém. de la Soc. méd. d. hôp. de Par., Par., 1920, s. 3, XLIV, 428.

PERNICIOUS ANEMIA

A CLINICAL STUDY OF ONE HUNDRED AND FIFTY CONSECUTIVE CASES WITH SPECIAL REFERENCE TO GASTRIC ANACIDITY

By Samuel A. Levine,

Assistant in Medicine, Harvard Medical School,

and

William S. Ladd,

Instructor in Medicine, The Johns Hopkins Medical School

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

This study was begun in 1915. Our interest was aroused at that time because we observed in all our cases of pernicious anemia an absence of free hydrocholoric acid in the gastric contents. For a long time it has been known that the absence of free hydrochloric acid is a frequent finding in this disease, although the actual incidence in the reports of various authors has differed considerably. In isolated cases studied over long periods of time, the achylia gastrica antedated the development of the anemia by several years. Thus K. Faber [1] noted achylia gastrica in three cases, eight, four and ten years before death from pernicious anemia. In each instance when the achylia was first observed the hemoglobin was over 90 per cent, and in each case the patient developed the picture typical of pernicious anemia long after the finding of anacidity. Very recently Friedenwald and Morrison [2] have given a good review of the conflicting evidence concerning the character of gastric secretion in pernicious anemia; in 74 per cent of their own 57 cases achylia was noted. The problem to be solved was whether, in arriving at the diagnosis, the presence or absence of free hydrochloric acid was possibly of as much value as some of the other acknowledged factors, such as the high color index of the blood or the presence of macrocytes in the smear.

We decided, therefore, upon a routine gastric analysis in all cases of possible pernicious anemia, and further, upon the repetition of the analysis during the progress of the disease, especially during remissions.

To obtain these data the Rehfuss tube was introduced. The fasting contents were taken; the tube was retained, an Ewald test meal given and samples taken at forty-minute intervals over a varying period of time. In a few cases, a test was made for the presence of pepsin.

We have observed in the clinic of this hospital 150 consecutive cases of pernicious anemia. We are including in this paper a brief discussion of several other points which we believe to be of sufficient interest to warrant this inclusion, namely, a discussion of seven special cases, the family history, racial discrepancies, syphilis and pernicious anemia, the occurrence of eosinophilia, the typical blood picture, unnecessary abdominal operations, the occurrence of gray hair and age and sex considerations.

The Gastric Secretion in Pernicious Anemia

As may be seen from Table 1, of the 143 cases of pernicious anemia with proved diagnosis, in 107 a gastric analysis was made one or more times. In a few of the cases the analyses cover a period of years. In one instance they were made on samples taken every 15 minutes for 2 hours and 30 minutes. In all but three cases there was no free hydrochloric acid. Hence it may be assumed that, as a rule, anacidity is constant and persistent throughout the disease. In the cases of five patients pepsin was absent in the seven analyses made. Since this series was completed pepsin has been found absent in most of the cases examined. Further data are being obtained on this point.

In the three cases in which some free hydrochloric acid was demonstrated, the following points are worth noting:

1. In case 58, there was a perfectly normal acidity but the post-mortem examination corroborated the diagnosis of pernicious anemia.

2. In case 117 the picture presented was typical of pernicious anemia. The patient had undergone three operations for a persistent bloody diarrhœa at one of which, nine years before admission, eleven inches of intestine had been removed. There was much difference of opinion as to the correct diagnosis. Finally "atypical anemia, primary anemia (?)" was agreed upon.

3. In case 124 the symptoms pointed to the presence of a tumor of the spinal cord. A subsequent operation disproved this assumption. Death followed one month later. In this instance, the first gastric analysis showed complete anacidity in all samples but the fourth, which gave a free HCl of 6.

TABLE 1

Serial number	Hospital number	Clinical diagnosis	Age	Sex	Wassermann	Birthplace	Eosinophilia, per cent	Gastric analysis *	Date of gastric analysis	Hemoglobin, per cent †	Family history	Tongue ‡	Hair §	Date of admission	Blood smear ‖	Follow-up notes
1	1791	Posterior-lateral sclerosis. Pernicious anemia.	46	M.	—	U. S.	1.5	? M 0 ? M 12	10-14-14	84	Neg.	T.	?	10- 6-14	S.	No note.
2	2133	Pernicious anemia.....	68	F.	—	Canada.	1	?	....	?	Tbc.	N.	?	1- 5-15	T.	No note.
3	1548	Pernicious anemia.....	41	F.	—	U. S.	18	?	....	?	Neg.	T.	?	8-18-14	T.	Splenectomy. Died, 3-20-16.
4	2282	Pernicious anemia.....	63	M.	—	U. S.	9	0 M 0 1 M 4 0 M 0-0-0	2- 6-15	29	Neg.	T.	G.	2- 5-15	T.	
	4067	Arteriosclerosis.....	.....	.....	.....	.....	10	0 M 4-14-12	1-30-16	30	.....	.....	.....	1- 9-16		Died, 6-15-17.
5	2049	Secondary anemia, ...	57	M.	—	U. S.	5.5	? M 0 M 1	12-27-14	40	Neg.	?	?	12-16-14	S.	
	2437	Pernicious anemia, Arteriosclerosis.	.....	.....	.....	.....	.....	? M 0 M 5	3- 8-15	32	.....	.....	.....	3- 5-15	T.	Died, October, 1915.
6	2808	? Pernicious anemia. Chronic arthritis of spine.	42	M.	—	U. S.	3	0 M 0	5-25-15	80	Neg.	?	?	5-18-15	S.	Died, January, 1917.
7	2848	Pernicious anemia. Chronic nephritis.	56	M.	—	U. S.	4	?	?	?	Neg.	?	W.	5-25-15	T.	January, 1917, working.
8	4181	Pernicious anemia.....	51	M.	—	Russia.	0	0 M ? 10 M								
								0 M 0-0-0 12 M 12-15-18 No pepsin.	5- 7-16	82						
							5	0 M 0-0 5 M 4-4 No pepsin.	10- 2-17	55	.....	.....	.....	.....	.....	Died, 8-13-18.
9	4316	Pernicious anemia.....	48	F.	—	Canada.	3	0 M 0-0-0 8 M 8-14-10 No pepsin.	3-16-16	52	Neg.	T.	?	3-13-16	T.	Died, June, 1916.
								0 M 0-0-0 13 M 9-11-13 No pepsin.	5-21-16	67						
10	4404	Pernicious anemia.....	60	F.	—	U. S.	4	0 M 0-0-0 12 M 20-15-34 No pepsin.	3-29-16	30	Cancer. Tbc.	T.	W.	3-27-16	T.	Died, 6-28-16. P. M., Pernicious anemia.
11	4565	Pernicious anemia.....	38	F.	—	Canada.	8	0 M 0 8 M 5	8- 9-16	88	Neg.	T.	?	4-26-16	T.	October, 1920, working; doing very well.
12	4719	Pernicious anemia.....	73	F.	—	U. S.	0	?	....	?	Neg.	T.	G.	5-24-16	T.	Died, 6-10-16. Pernicious anemia.
13	4609	Pernicious anemia.....	73	F.	—	U. S.	0	0 M 0-0 15 M 9-12	5- 5-16	29	Cancer.	S.	W.	5- 4-16	T.	
								0 M 0	7- 3-16	37	.....	.....	.....	.....	.....	Died, November, 1916.
14	4748	Pernicious anemia.....	42	M.	—	U. S.	3	?	....	?	Tbc.	T.	G.	5-29-16	T.	Died, 7-27-16. P. M., Pernicious anemia.
15	4649	Pernicious anemia.....	63	M.	—	U. S.	4	? M 0-0-0 M 4-8-15 0 M 0	5-22-16	35	Neg.	T.	G.	5-18-16	T.	
								8 M 5	9- 1-16	104	.....	.....	.....	.....	.....	Died, 12-26-16.
16	42	Pernicious anemia.....	44	F.	?	Engl.nd.	0	?	....	?	Neg.	?	?	4-25-13	T.	No note.
17	1169	Pernicious anemia.....	35	F.	—	U. S.	0	?	....	?	Neg.	S.	N.	5- 7-14	T.	Doubtful diagnosis, Pernicious anemia.
		Purpura	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	January, 1920, came in for bleeding from varicose vein.
18	1132	Pernicious anemia. Cancer of stomach.	44	M.	—	Sweden.	4	? M 0 M 24	5- 7-14	32	Cancer. Tbc.	?	?	4-29-14	T.	X-ray showed definite cancer of stomach. Two diagnoses here. Died; date unknown.
19	1324	Pernicious anemia. Acute pericarditis.	51	F.	—	U. S.	5	0 M 0 0 M 13	9-22-16	111	Neg.	T.	W.	6- 9-14	T.	
	10380	.....	.....	.....	.....	.....	.....	0 M 0-0-0 0 M 8-10-8	1-25-19	39	.....	.....	.....	1-24-19	.....	Died, April, 1919.
20	1327	Pernicious anemia ? Cancer of stomach ?	54	F.	—	U. S.	0	? M 0 M 1	7- 5-14	78	Tbc.	?	W.	8-18-14	At.	May, 1915, hemoglobin, 95%.
21	1544	Pernicious anemia.....	44	M.	—	U. S.	6	?	?	?	Neg.	T.	W.	8-17-14	T.	Died, August, 1916.
22	2789	Pernicious anemia ?.....	32	F.	—	Canada.	0	?	....	?	Neg.	?	?	5-14-15	T.	9-29-16, hemoglobin, 121%; smear normal. October 10, 1920, doing fairly well.
23	2788	Pernicious anemia.....	40	F.	—	Canada.	2	? M 0 M 4	5-14-15	35	Neg.	T.	?	5-13-15	T.	Splenectomy. Died, March 28, 1918.
24	3045	Pernicious anemia; syphilis. Mitral stenosis. Acute endocarditis.	31	M.	++	U. S.	7	?	....	?	Neg.	T.	?	7- 5-15	T.	Died, 5-7-17. P. M., Pernicious anemia, mitral stenosis, acute pericarditis.
	6395	.....	.....	.....	.....	.....	0	0 M 0-0-0 4 M 12-8-4	4- 8-17	34	.....	.....	.....	4- 5-17	.....	Acute peritonitis.
25	3005	Pernicious anemia. Asthma. Chronic nephritis?	49	M.	—	U. S.	17	?	....	?	Tbc.	T.	G.	7-17-15	T.	Died, 12-7-15.
26	2984	Pernicious anemia.....	47	F.	—	U. S.	24	0 M 0 M 10	6-23-15	23	Neg.	T.	G.	6-22-15	T.	Died, 12-13-17.
27	3096	Pernicious anemia.....	50	F.	—	U. S.	17	0 M 0 0 M 0	8-19-15	40	Cancer.	T.	G.	7-17-15	T.	
							12	6 M 11	10-10-16	70						
	5913	.....	.....	.....	.....	.....	0	0 M 0-0-0 0 M 6-6-4	1-11-17	20	.....	.....	.....	1- 8-17	.....	January, 1921. Doctor replies that patient was doing well when last seen, but does not say when.
28	3139	Pernicious anemia.....	59	F.	—	England.	16	0 M 0 23 M 18	8-30-15	35	Tbc. Cancer.	T.	W.	7-28-15	T.	10-28-15. Splenectomy.
	4217	.....	.....	.....	.....	.....	10	0 M 0-0-0 8 M 10-8-8 No pepsin.	2-24-16	36	.....	.....	.....	2-23-16	.....	Died, 7-20-16.
29	4935	Pernicious anemia.....	55	M.	—	England.	5	0 M 0-0-0 14 M 12-10-8	7- 2-16	70	Neg.	T.	W.	7- 2-16	T.	Died, 12-26-17.

* Upper figure is the free HCl, lower is the total acid, expressed in c. c. of N-10 HCl per 100 c. c. stomach contents. M indicates test meal.
† Hemoglobin determinations made the same day as gastric analysis or within a few days. ‡ T = typical. S = suggestive. N = normal.
§ G = gray. W = white. N = normal. ‖ T = typical. S = suggestive. At = atypical.

TABLE 1—CONTINUED

Serial number	Hospital number	Clinical diagnosis	Age	Sex	Wassermann	Birthplace	Eosinophilia, per cent	Gastric analysis*	Date of gastric analysis	Hemoglobin, per cent†	Family history	Tongue‡	Hair§	Date of admission	Blood smear‖	Follow-up notes
30	4478	Pernicious anemia.....	38	F.	—	Ireland.	5	0 M 0-0-0 8 M 18-20-20 0 M 0 6 M 20 0 M 0-0-0 4 M 8-6-6	4-12-16 4-21-17 10- 7-20	28 85 70	Neg.	T.	G.	4- 8-16	T.	October 7, 1920. Tongue smooth. Working.
31	5070	Pernicious anemia.....	47	M.	—	U. S.	7	0 M 0-0-0 24 M 20-22-18	8-10-16	67	Neg.	T.	G.	8- 7-16 12- 2-13	T.	October 11, 1920. In fair health; has neuritis.
32	589	Chronic nephritis. Hypertension. Arteriosclerosis.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
	5169	Pernicious anemia; chronic nephritis; chronic myocarditis. ? Lead poisoning.	56	M.	—	Ireland.	3	0 M 0 8 M 10	9-27-16	67	Tbc.	T.	?	8-21-16	T.	Died, May 8, 1917.
33	5174	Pernicious anemia. Chronic nephritis. Chronic uremia. Insolation.	49	F.	—	England.	0	?	....	?	Neg.	S.	G.	8-22-16	T.	Died, 8-25-16. Terminal temp. 107°. ? Sunstroke. Very hot day. No P. M.
34	4949	Pernicious anemia.....	47	M.	—	U. S.	8	0 M 0-0-0 14 M 12-24-14	7-10-16	45	Tbc.	T.	G.	7- 8-16	T.	No note.
35	3435	Pernicious anemia.....	48	F.	—	U. S.	7	? M 0-0-0 M 3-15-6 0 M 0 5 M 10	10-12-15 9-19-16	29 61	Cancer.	T.	N.	10- 8-15	T.	Died between May, 1917, and December, 1918.
36	3491	Pernicious anemia.....	47	M.	—	U. S.	4	0 M 0 4 M 8 0 M 0-0-0 4 M 13-8	10-24-15 10-30-19	40 80	Neg.	T.	N.	10-20-15	T.	Sept., 1917. Hemoglobin 112%. Doing heavy work. 9-6-20. Feels well; treated by a quack.
37	3538	Pernicious anemia.....	54	M.	—	Sweden.	3	M 0 M 8 0 M 0 6 M 14	10-28-15 9-18-16	37 124	P. A.	S.	G.	10-28-15	S.	Died, January 26, 1920.
38	3636	? Pernicious anemia. ? Cancer of stomach.	66	M.	—	Ireland.	9	0 M 0 M 1 0 M 0-0-0-0 M 3-6-8-10 0 M 0-0 6 M 5-1 0 M 0 ? M 9	11-18-15 11-28-15 2-11-16 9-18-16	50 60 78 91	Cancer.	S.	G.	11-17-15	S.	Atypical case. August, 1917. Hemoglobin, 80%. Cramps in legs. Is working. This discredits diagnosis of cancer. Died, August 23, 1919.
39	1784	Pernicious anemia.....	42	F.	—	Ireland.	6	.....	....	?	Neg.	T.	G.	10-19-14	T.	Died, 2-25-16.
40	2834	Pernicious anemia.....	31	M.	—	Canada.	1	Free HCl in vomitus, 0	....	.....	Neg.	T.	N.	5-22-15	T.	Died, 6-23-15.
41	3768	Pernicious anemia. Hemorrhagic stomatitis.	30	F.	—	U. S.	2	?	....	?	Neg.	N.	N.	12-11-15	S.	Died, 1-15-16.
42	106	Pernicious anemia. Chronic nephritis. ?	59	F.	—	U. S.	6	?	....	?	Cancer.	T.	?	5-23-13	T.	Died, 11-6-15.
43	135	Pernicious anemia.....	61	F.	—	U. S.	7	?	....	?	Neg.	?	?	6-11-13	T.	Splenectomy. Died during 1915.
44	780	Pernicious anemia.....	44	F.	—	England.	7	?	....	?	Neg.	T.	?	1- 3-14	T.	Died, 2-20-15.
45	881	Pernicious anemia.....	64	F.	—	Canada.	6	?	....	?	Tbc.	?	?	2-26-14	T.	Died, 12-6-15.
46	1130	Pernicious anemia.....	51	M.	?	U. S.	1	?	....	?	Neg.	?	?	4-29-14	T.	Died, 5-1-14. P. M., aplastic bone marrow.
47	1413	Pernicious anemia.....	38	F.	—	U. S.	2	?	....	?	Neg.	?	?	7-10-14	T.	Died, 1-5-15. P. M., pernicious anemia.
48	1410	Pernicious anemia.....	72	M.	—	U. S.	1	?	....	?	Neg.	?	?	7-10-14	T.	Died, August 31, 1916 (or 1915).
49	1280	Pernicious anemia. Hemophilia.	26	M.	—	U. S.	4	?	....	?	Neg.	?	?	6- 3-14	T.	Died, 9-2-14.
50	2680	Pernicious anemia. Eosinophilia, cause unknown.	64	F.	—	U. S.	28	0 M 0 M 14	5- 8-15	25	Neg.	S.	?	4-23-15	T.	No note.
51	3063	Pernicious anemia. Exhaustive psychosis.	51	F.	—	Canada.	3	Vomitus No. M 0 Free HCl M 6	7-11-15	36	Cancer.	?	G.	7- 9-15	T.	Died, 6-22-15.
52	3718	Pernicious anemia.....	36	F.	—	Canada.	6	0 M 0-0-0-0 M 4-3-5-4 0 M 0 6 M 9	12-11-15 9-19-16	35 87	P. A.	T.	N.	12- 2-15	T.	Died, 1917.
53	3690	Pernicious anemia. Syphilis.	68	M.	++	U. S.	9	0 M 0-0-0 M 22-10-4 0 M 0-0-0 M 2-2-3 0 M 0-0-0 No pepsin.	11-29-15 1-19-16 3-20-16	21 93 72	Neg.	T.	W.	11-27-15	T.	Died, Nov. 27, 1916. Received vigorous anti-syphilitic treatment.
54	3863	Pernicious anemia. Syphilis.	43	M.	++	Canada.	8	0 M 0-0-0 8 M 11-11-18 0 M 0 0 M 10	1-13-16 3-21-17	28 88	Cancer. Anemia.	T.	G.	12-29-15	T.	Received anti-luetic treatment. Died, April, 1917.
55	4063	Pernicious anemia. Syphilis.	63	F.	++	U. S.	7	0 M 0-0-0 0 M 4-3 0 M 0-0-0 10 M 27-10-10	1-30-16 3- 3-16	48 90	Anemia.	T.	G.	1-20-16	T.	September 23, 1920. Been very well since leaving hospital.
56	4430	Pernicious anemia. Chronic Nephritis. Hypertension. Chronic Myocarditis. ? Angina Pectoris.	60	F.	—	U. S.	0	0 M 0-0-0 15 M 20-18-18	4- 1-16	78	Tbc.	S.	G.	3-31-16	S.	Died, 9-6-17. P. M., pernicious anemia, chronic nephritis and postero-lateral sclerosis.
57	4292	Pernicious anemia.....	28	F.	—	U. S.	1	0 M 0-0-0 10 M 10-20-15	3-10-16	22	Neg.	T.	G.	3- 8-16	T.	
	5211	.....	.....	.....	.....	.....	.....	0 M 0-0-0 3 M 2-4-4	10-18-16	85	.....	.....	.....	8-28-16	.....	Died, May 5, 1917.

* Upper figure is the free HCl, lower is the total acid, expressed in c. c. of N-10 HCl per 100 c. c. stomach contents. M indicates test meal.
† Hemoglobin determinations made the same day as gastric analysis or within a few days. ‡ T = typical. S = suggestive. N = normal.
§ G = gray. W = white. N = normal. ‖ T = typical. S = suggestive. At = atypical.

TABLE 1—CONTINUED

Serial number	Hospital number	Clinical diagnosis	Age	Sex	Wassermann	Birthplace	Eosinophilia, per cent	Gastric analysis*	Date of gastric analysis	Hemoglobin, per cent †	Family history	Tongue ‡	Hair §	Date of admission	Blood smear ‖	Follow-up notes
58	5330	Pernicious anemia. B. pyocyaneus, generalized infection.	58	F.	—	U. S.	0	0 M 22 36-50 22 M 54-60-62	9-22-16	63	Neg.	T.	G.	9-20-16	T.	Died, 10-19-16. P. M., pernicious anemia, fibrous pericarditis and pleuritis. Autopsy stomach contents. No free HCl.
59	5409	Pernicious anemia. Chronic cystitis. Psychosis, symptomatic.	45	F.	—	Ireland.	1	0 M 0-0-0 M 3	10-16-16	20	Neg.	T.	G.	1[illegible]-7-16	T.	No note.
60	5485	Pernicious anemia.....	21	F.	—	U. S.	3	0 M 0-0-0 2 M 6-4-20 0 M 0-0-0 M 3-9-13	11-24-16 12-18-16	56 90	P. A.	T.	N.	10-28-16	T.	Considered Tbc. at Sharon. Died, December 30, 1917.
61	5585	Pernicious anemia.....	54	M.	—	U. S.	2	0 M 0-0-0 8 M 14-10-10	11-14-16	80	Tbc.	T.	G.	11-12-16	At.	June, 1918, about the same.
62	5610	Pernicious anemia. Chronic nephritis.	65	F.	—	U. S.	1	0 M 0-0-0 M 14	11-17-16	25	Neg.	T.	G.	11-16-16	T.	Colored. Died during 1917.
63	5657	Pernicious anemia. Chronic nephritis.	62	F.	—	U. S.	0	0 M 0-0-0 6 M 10	11-25-16	30	Neg.	T.	W.	11-14-16	T.	Died, February 26, 1918.
64	5500	Pernicious anemia.....	43	F.	—	Canada.	1	0 M 0-0-0 4 M 2-4	11-15-16	73	Neg.	N.	?	11-13-16	at.	Died, April, 1917.
65	5377	Pernicious anemia.....	29	M.	—	U. S.	4	0 M 0-0-0 14 M 24-24-12	10-5-16	29	Neg.	T.	G.	9-30-16	T.	Died, 3-21-17. P. M., Pernicious anemia; acute peritonitis; acute nephritis.
66	5548	Pernicious anemia.....	48	M.	—	U. S.	5	0 M 0 0 M 5 No pepsin. 0 M 0-0-0 40 M 70-22-26	1910 11-5-16	90 42	P. A.	T.	G.	11-3-16	T.	Diagnosis: Gastric neurosis, due to overwork and worry, 1910. Died, October, 1918.
67	6207	Pernicious anemia. Pulmonary emphysema.	66	F.	—	Ireland.	1	? M 0-0-0 M 6-14	2-27-17	25	Neg.	T.	G.	2-25-17	T.	Died, 3-5-17. No P. M.
68	6142	Pernicious anemia.....	38	F.	—	U. S.	8	0 M 0-0-0 10 M 4-4	2-16-17	50	Cancer.	T.	G.	2-14-17	T.	Died September 13, 1918.
69	5811	Pernicious anemia? Addison's Disease? Tbc. Retroperitoneal nodes.	42	M.	—	Sweden.	0	0 M 0-0-0 12 M 14-8-10	12-22-16	70	Tbc.	S.	N.	12-20-16	T.	Atypical case. Died, 4-19-17. P. M., nothing except hyperplasia of mesenteric glands and lymphatics of small intestine.
70	6017	Pernicious anemia.....	52	F.	—	Russia.	4	? M 0 M 8	1-25-17	40	?	T.	G.	1-22-17	T.	Had psychosis. No note.
71	6394	Pernicious anemia.....	57	M.	—	U. S.	0	0 M 0-0-0 10 M 12-8-8	4-7-17	28	Neg.	T.	G.	4-5-17	T.	Died, 4-16-17.
72	6364	Pernicious anemia. ? Combined degeneration of spinal cord.	53	M.	—	Sweden.	1	0 M 0-0-0 10 M 10-25-16	4-2-17	60	Neg.	T.	G.	3-31-17	T.	Died, May, 1917.
73	1729	Pernicious anemia.....	53	F.	—	U. S.	3	M 0 M 13	10-11-14	94	Neg.	T.	W.	10-6-14 3-1-17	N. T.	Not diagnosed pernicious anemia at this time. Anacidity found with normal blood; twenty months later had typical pernicious anemia. Died, August, 1919.
74	6679	Pernicious anemia. ? Mitral stenosis and mitral insufficiency.	48	F.	—	U. S.	0	?	....	?	Cancer.	T.	W.	5-25-17	T.	Died before August, 1918.
75	6632	Pernicious anemia. Furunculosis.	74	M.	—	Germany.	3	0 M 0-0-0 16 M 12-12-16	5-26-17	40	Neg.	T.	G.	5-18-17	T.	Atypical case, white count of 14,000. X-ray showed filling defect of lesser curvature. Died, November 14, 1917.
	6051	.....	.....	.....	.....	.....	.....	0 M 0-0 5 M 6-0	7-30-17	30						
76	6600	Pernicious anemia. Fractured rib.	46	F.	++	Ireland.	4	0 M 0-0-0 10 M 10	5-14-17	40	Neg.	S.	G.	5-12-17	T.	Treatment: diarsenol. June 19, 1920, fairly well.
77	5990	Pernicious anemia. Chronic nephritis.	53	M.	—	U. S.	4	0 M 0-0-0 6 M 4-6	1-20-17	28	Tbc.	T.	G.	1-19-17	T.	Died, 8-12-17.
78	7005	Pernicious anemia. Combined degeneration of spinal cord.	57	M.	—	U. S.	8	0 M 0-0-0-0 0 M 10-6-6	7-31-17	60	Tbc.	T.	G.	7-30-17	T.	Died, May 29, 1920.
79	7072	Pernicious anemia. Mitral stenosis; mitral insufficiency.	42	M.	—	Ireland.	1	0 M 0-0 25 M 17-22	8-16-17	31	Neg.	T.	G.	8-14-17	T.	Died, about June, 1918.
80	7202	Pernicious anemia.....	65	M.	—	England.	5	0 M 0-0-0 9 M 12-13-13	9-10-17	46	Neg.	T.	W.	9-8-17	T.	Died suddenly, 10-2-17. Delirious. P. M., pernicious anemia and pachymeningitis.
81	7256	Pernicious anemia. Mitral stenosis; mitral insufficiency. Paranoid psychosis.	40	F.	—	Sweden.	3	?	....	?	Cancer.	?	N.	9-20-17	T.	9-21-20, no note.
82	7160	? Pernicious anemia. Combined degeneration of spinal cord.	44	M.	—	Canada.	3	?	....	?	Neg.	T.	N.	8-30-17	S.	Died, October, 1917.
83	6974	Pernicious anemia. Arteriosclerosis.	59	F.	—	U. S.	6	0 M 0-0-0 10 M 16-12-14	7-25-17	45	Neg.	S.	G.	7-23-17	T.	Died, 4-26-18.
84	7110	Pernicious anemia.....	46	M.	—	U. S.	2	0 M 0-0-0 13 M 14-13-24	8-21-17	29	Tbc.	N.	G.	8-20-17	T.	Died, about September, 1918.
85	6882	Pernicious anemia.....	51	M.	—	U. S.	9	0 M 0-0-0 M 9-16-13	7-7-17	30	Neg.	N.	G.	7-5-17	T.	Died, December 30, 1918.
86	7207	Pernicious anemia.....	58	F.	—	U. S.	3	0 M 0-0 3 M 12-12	9-10-17	40	Neg.	T.	G.	9-8-17	T.	Died, latter part of 1919.
87	7434	Pernicious anemia. Lateral sclerosis.	40	F.	+	U. S.	4	0 M 0-0 22 M 20-20	10-22-17	68	P. A.	N.	N.	10-20-17	T.	Died, June 3, 1918.
88	7026	? Pernicious anemia.....	45	F.	—	Ireland.	4	0 M 0-0-0 0 M 10-0	8-8-17	45	Neg.	T.	G.	8-6-17	S.	9-21-20. Was in fair health in spring of 1920.
89	7493	Pernicious anemia. Internal hemorrhoids.	58	M.	—	U. S.	2	0 M 0-0-0 4 M 5-6-6	11-3-17	50	Neg.	N.	G.	11-1-17	T.	Died, October 14, 1920.
90	7745	Pernicious anemia ?.....	65	F.	—	U. S.	0	0 M 0-0-0 5 M 4-4-5	12-27-17	65	Tbc.	T.	G.	12-22-17	S.	Sept., 1920. Living, but in poor health. Unable to use legs much.
91	7719	Pernicious anemia? Lateral sclerosis?	35	F.	—	U. S.	4	?	....	?	Neg.	S.	G.	10-17-17	S.	March 20, 1919. Condition about the same.
92	7736	Pernicious anemia.....	29	F.	—	Canada.	8	?	....	?	Neg.	N.	N.	12-20-17	T.	Died, May 10, 1918. Mentally confused, with ataxic paraplegia.
93	8220	Pernicious anemia.....	58	M.	—	U. S.	0	0 M 0-0-0 15 M 17-18-20	3-5-18	48	Tbc.	T.	W.	3-4-18	..	Died, end of March, 1918.

* Upper figure is the free HCl, lower is the total acid, expressed in c. c. of N-10 HCl per 100 c. c. stomach contents. M indicates test meal.
† Hemoglobin determinations made the same day as gastric analysis or within a few days. ‡ T = typical. S = suggestive. N = normal.
§ G = gray. W = white. N = normal. ‖ T = typical. S = suggestive. At = atypical.

TABLE 1—CONTINUED

Serial number	Hospital number	Clinical diagnosis	Age	Sex	Wassermann	Birthplace	Eosinophilia, per cent	Gastric analysis*	Date of gastric analysis	Hemoglobin, per cent †	Family history	Tongue ‡	Hair §	Date of admission	Blood smear ‖	Follow-up notes
94	8217	Pernicious anemia.....	56	F.	—	U. S.	5	0 M 0-0-0 M 17-23-13	3- 5-18	35	Neg.	S.	G.	3- 4-18	T.	Died, May 28, 1918.
95	8192	Pernicious anemia.....	53	M.	—	U. S.	0	0 M 0-0-0 17 M 9-6-6	3- 6-18	40	Neg.	S.	N.	2-28-18	T.	Died, about May, 1918.
96	8540	Pernicious anemia.....	61	M.	—	U. S.	3	? M 0-0-0 M 9-7-12	4-17-18	50	P. A.	T.	G.	4-20-18	T.	
								0 M 0-0-0-0-0 -0-0-0-0-0 M 6-6-5-6-5 -5-12-12 -12-8 Every fifteen minutes.	3-24-19	29	.....	.....	.....	3- 5-19	..	Died, October 28, 1919.
97	8448	Pernicious anemia.....	62	F	—	U. S.	4	0 M 0-0 8 M 6	4-11-18	30	Cancer.	N.	W.	4- 9-18	T.	8-30-20. Fine; smear normal.
98	8865	Pernicious anemia.....	59	M.	—	U. S.	2	?	....	?	Neg.	?	W.	6-23-18	S.	Died, 6-27-18. P. M., Pernicious anemia and healed Tbc.
99	8817	Pernicious anemia.....	62	M.	—	U. S.	4	?	....	?	Tbc.	T.	G.	6-13-18	T.	Died, October 9, 1918.
100	8913	Pernicious anemia.....	48	F.	—	England.	7	0 M 0-0-0 8 M 10-11-14	7-10-18	85	Neg.	T.	G.	7- 3-18	S.	Died, May, 1919.
101	9017	Pernicious anemia. Chronic myocarditis. Hypertension.	71	F.	—	U. S.	3	? M 0-0-0	8-22-18	00	Neg.	T.	W.	7-22-18	T.	Died, spring of 1919.
102	9102	Pernicious anemia.....	54	F.	—	England.	5	0 M 0-0-0 M 2-2-5	8- 8-18	23	Neg.	N.	W.	8- 9-18	T.	Died, 2-21-19. P. M., Pernicious anemia and chronic nephritis.
103	9291	Pernicious anemia.....	63	F.	—	U. S.	1	0 M 0	9-17-18	20	Cancer.	N.	G.	9-16-18	T.	Died, February 21, 1919.
104	9774	Pernicious anemia. Gas bacillus infection; terminal.	41	M.	—	U. S.	1	?	....	?	Neg.	N.	N.	10-30-18	At.	Died, 11-5-18. P. M., Pernicious anemia and gas bacillus infection.
105	9792	Pernicious anemia.....	52	M.	—	Ireland.	6	0 M ? 0-0 20 M 16-20	11- 9-18	40	Neg.	S.	G.	11- 5-18	T.	Is a rubber worker and exposed to chemical fumes. April 17, 1920, feels fair. Hemoglobin 60%. ? Anemia, due to chemicals.
106	9900	Pernicious anemia.....	33	F.	—	U. S.	0	0 M 0-0-0 8 M 2-10-3	11-23-18	55	P. A.	T.	N.	11-21-18	T.	September, 1920. Quite well. Working.
107	10295	Pernicious anemia.....	54	M.	—	Canada.	1	0 M 0-?-0 5 M 0 -12	1-16-19	18	Neg.	T.	G.	1-14-19	T.	Died some time before June, 1920.
108	10324	Pernicious anemia. ? Tuberculous pleurisy.	49	M.	—	U. S.	3	?	....	?	Neg.	T.	G.	1-18-19	T.	Died, 2-14-20.
109	8345	Pernicious anemia.....	30	F.	—	Denmark.	4	0 M 0-0-0 2 M 5-6-18 0 M 0-0-0	4-27-18	75	Cancer.	S.	G.	3-26-18	T.	
								10 M 40-0-10	1-25-19	..	.....	..	..	1-18-19	..	Died, January, 1920.
110	10748	Pernicious anemia.....	47	F.	—	U. S.	1	0 M 0-0-0 20 M 16-0-10	3-28-19	29	Neg.	T.	W.	3-26-19	T.	September, 1918. Dr. F. T. Lord found blood normal. Died Oct. 23, 1918.
111	10630	Pernicious anemia. ? Cholelithiasis.	71	M.	—	U. S.	5	0 M 0-0-0 5 M 50-60	3- 8-19	65	Neg.	S.	W.	3- 6-19	S.	1-7-20. Hemoglobin, 90%. Good condition. October, 1920, in fair health.
112	10691	Pernicious anemia.....	36	F.	—	Sweden.	3	0 M 0-0-0 22 M 8-6-8	3-18-19	31	Neg.	T.	N.	3-17-19	T.	No note.
113	10705	Pernicious anemia.....	61	F.	—	Alsace Lorraine.	5	0 M 0 M 4	3-20-19	54	Neg.	N.	G.	3-19-19	T.	Died, June 23, 1919.
114	10635	Pernicious anemia.....	50	F.	—	U. S.	8	0 M 0 4 M	3-10-19	24	Neg.	S.	G.	3- 6-19	T.	Died, 4-10-20. P. M., Pernicious anemia.
115	11005	Pernicious anemia.....	71	F.	—	Canada.	0	0 M 0-0	5- 5-19	17	Tbc.	T.	W.	5- 3-19	T.	Died, May 24, 1919, of pernicious anemia.
116	10939	Pernicious anemia. Combined degeneration of spinal cord.	36	F.	—	U. S.	0	0 M 0-0-0 6 M 4-4-4	4-26-19	51	Neg.	N.	N.	4-23-19	S.	Died, 10-30-19.
117	10872	Anemia (severe, atypical, ? pernicious); chronic diarrhea.	38	F.	—	Canada.	1	4 M 28-30-14 28 M 56-60-34 0 M 24-0-0	4-13-19	63	Neg.	T.	N.	4-12-19	T.	Atypical case. Nine years ago 11 inches of gut removed; two other operations for bloody diarrhea.
								4 M 58-20-8	4-23-19	70						
118	10811	Pernicious anemia. Paralysis of facial nerve.	52	M.	—	Canada.	10	0 M 0-0-0 10 M 8-16-10	4- 8-19	22	Tbc.	S.	G.	4- 4-19	T.	July 9, 1919. Hemoglobin 80%. Well. Died, 1-26-20.
119	11201	Pernicious anemia.....	43	M.	—	U. S.	3	0 M 0-0-0 6 M 13-10-10	3-12-17	93	Neg.	N.	G.	6- 4-19	T.	Died, 6-5-19. P. M., Pernicious anemia, postero-lateral sclerosis and healed pulmonary tuberculosis.
120	11408	Pernicious anemia.....	48	F.	—	U. S.	0	0 M 0-0-0 25 M -10-25	7- 9-19	55	Neg.	N.	G.	7- 8-19	T.	Died, July 23, 1920.
121	11503	Pernicious anemia. ? Chronic myocarditis.	54	M.	—	U. S.	1	0 M 0-0-0 7-12-4-3	7-26-19	35	P. A.	T.	G.	7-24-19	T.	Died, June, 1920.
122	11822	Pernicious anemia.....	58	F.	—	Italy	3	0 M 0-0-0 14 M 22-8-2	9-12-19	45	Cancer.	T.	N.	9-11-19	T.	September, 1920. Condition the same.
123	11527	Pernicious anemia. Subacute infectious arthritis.	45	F.	—	Russia.	9	0 M 0-0-0	8- 1-19	85	Neg.	N.	G.	7-29-19	T.	
	13771	.....	.....	.....	.....	.....	.....	0 M 0-0-0 10 M 10-5	6-16-20	65	.....	.....	.....	6-14-20	.....	No note.
124	11502	? Tumor of spinal cord. ? Pernicious anemia.	63	M.	—	Canada.	0	0 M 0-0-0 10 M 20-42-67	7-26-19	65	Cancer.	N.	G.	7-24-19	At.	Operation by Dr. Cushing ? Spinal cord tumor. Died about January, 1920.
	10929	.....	.....	.....	.....	.....	.....	0 M 0-0-0-6 10 M 20-42- 16-32	7-30-19	65						
125	12013	Pernicious anemia.....	49	M.	—	U. S.	0	?	....	?	P. A. Tbc.	T.	G.	10-11-19	S.	Died, November 19, 1919.
126	11829	Pernicious anemia.....	55	F.	—	U. S.	6	0 M 0-0-0 6 M 23-16	9-14-19	35	Neg.	T.	W.	9-13-19	T.	Died, December 13, 1919.
127	11999	Pernicious anemia. ? Sprue (recovered).	53	M.	—	U. S.	9	0 M 0-0-0 0 M 0-0-0	9-11-19	30	Neg.	T.	G.	9- 7-19	S.	Died, 12-8-19. P. M., Bone marrow, hyperplasia.
128	12208	Pernicious anemia.....	56	F.	—	U. S.	3	0 M 0-0-0	11- 8-19	25	Neg.	T.	N.	11- 6-19	At.	No note.
129	12313	Pernicious anemia.....	61	F.	—	U. S.	12	0 M 0-0-0 15 M 25-25-30	11-22-19	55	Cancer. Tbc.	T.	G.	11-20-19	T.	Died, 12-4-19. P. M., Pernicious anemia.

* Upper figure is the free HCl, lower is the total acid, expressed in c. c. of N-10 HCl per 100 c. c. stomach contents. M indicates test meal.
† Hemoglobin determinations made the same day as gastric analysis or within a few days. ‡ T = typical. S = suggestive. N = normal.
§ G = gray. W = white. N = normal. ‖ T = typical. S = suggestive. At = atypical.

TABLE 1—CONTINUED

Serial number	Hospital number	Clinical diagnosis	Age	Sex	Wassermann	Birthplace	Eosinophilia, per cent	Gastric analysis*	Date of gastric analysis	Hemoglobin, per cent†	Family history	Tongue‡	Hair§	Date of admission	Blood smear‖	Follow-up notes
130	12322	Pernicious anemia. Vitiligo.	56	F.	—	Canada.	5	0 M 0-0	11-23-19	55	Cancer. Tbc.	S.	G.	11-21-19	T.	Doing pretty well. 8-30-20.
131	11710	Pernicious anemia.....	42	M.	—	U. S.	11	0 M 0-0-0	?	?	Neg.	T.	N.	9-18-19	S.	No note.
132	13032	Pernicious anemia.....	50	F.	—	U. S.	4	0 M 0-0-0 10 M 2-5-9	2- 4-20	85	Tbc.	T.	G.	2-23-20	S.	No note.
133	12607	Pernicious anemia. Arterio sclerosis.	59	M.	—	U. S.	0	0 M 0-0-0 8 M 17-30-20	1-29-19	45	Cancer.	T.	G.	12-28-19	S.	No note.
134	12633	Pernicious anemia. Ataxic paraplegia. Hypertension.	42	M.	—	U. S.	0	0 M 0-0-0 2 M 7-11-12	1- 7-20	100	Neg.	N.	G.	1- 1-20	S.	No note.
135	12699	Pernicious anemia. Ataxic paraplegia. Arterio-sclerosis.	55	F.	—	Canada.	6	0 M 0-0-0	1-17-20	84	Neg.	S.	G.	1-12-20	S.	No note.
136	12725	Pernicious anemia.....	67	F.	—	U. S.	1	0 M 0-0	1-17-20	35	Neg.	S.	W.	1-15-20	T.	No note.
137	12285	Pernicious anemia. Chronic myocarditis. Acute pulmonary œdema.	55	F.	—	Canada.	1	?	....	?	Neg.	T.	?	10-10-19	T.	No note.
138	13167	? Pernicious anemia. Cardiac hypertrophy.	41	F.	—	Ireland.	2	0 M 0-0-0 37 M 10-16-3	3-16-20	60	Neg.	N.	G.	3-15-20	S.	No note.
139	13226	Pernicious anemia. Diabetes mellitus.	50	F.	—	Denmark.	5	?	....	?	Neg.	N.	G.	3-24-20	T.	No note.
140	13266	Pernicious anemia. ? Mitral stenosis and mitral insufficiency.	40	F.	—	Canada.	1	?	....	?	Tbc.	N.	G.	3-20-20	T.	Transfused in 1917 for anemia. September 1, 1920, not doing well.
141	13635	Pernicious anemia.....	52	F.	+	Canada.	0	0 M 0-0-0 2 M 10-10-8	5-26-20	44	Cancer. Tbc.	T.	G.	5-24-20	S.	No note.
142	13262	Pernicious anemia. Chronic bronchitis. ? Syphilis.	69	F.	+±	U. S.	2	0 M 0-0-0 4 M 3-3-4	4-10-20	55	Neg.	N.	G.	3-29-20	S.	No note.
143	13783	? Pernicious anemia.....	59	F.	—	Armenia.	4	0 M 0-0-0 3 M 3-12-11	6-16-20	31	Neg.	N.	G.	6-15-20	S.	Atypical: had great deal of diarrhea. ? Pellagra or sprue or cancer.
144	294	Pernicious anemia.....	37	M.	—	Canada.	0	0 M 28 16 M 68	7-21-16	74	?	T.	N.	8-23-13	S.	Sept., 1920. Well and working.
145	3709	Dibothriocephalus latus..	33	F.	—	Sweden.	8	0 M 0 12 M 6 0 M 0-0 9 M 12-5	12- 2-15 8- 9-16	40 124	Neg.	T.	N.	11-30-15	T.	Four worms delivered. Typical pernicious anemia picture. May, 1918. Well.
146	3729	? Pernicious anemia. ? Anemia secondary to gasoline fumes.	17	M.	—	U. S.	20	0 M 0-0-0 8 M 36-16-6 0 M 0-0-0 0 M 5-14-14 0 M 0-0-0 0 M 16-23-5 0 M 0-12 8 M 18-43	12- 8-15 1-15-16 2- 4-16 10- 8-16	37 82 126 116	Neg.	T.	N.	12- 4-15	T.	 September, 1920. Well ever since discharge.
147	6225	Chronic nephritis. Chronic uremia. Pernicious anemia.	62	F.	—	U. S.	..	0 M 0-0-8 0 M 28-22-32	3- 1-17	41	Neg.	N.	G.	2-28-17	S.	Atypical case. White count 46,000. Phthalein 0%. Died, 3-19-17. P. M., acute pericarditis, pleuritis, peritonitis and enteritis; chronic cholecystitis and peritonitis; chronic vascular nephritis, but nothing suggestive of pernicious anemia.
148	6375	Pulmonary tuberculosis. Renal tuberculosis. ? Pernicious anemia. Stomatitis.	45	F.	—	Canada.	4	0 M 0-?-0 10 M 0- 20	4- 6-17	78	Cancer.	S.	N.	4- 2-17	S.	Died, March, 1918. P. M., tuberculosis of lung, intestines and kidney; sprue, but no pernicious anemia.
	7297	Sprue, pulmonary tuberculosis. Secondary anemia.														
149	6872	? Cancer of cæcum. ? Pernicious anemia.	42	F.	—	U. S.	1	0 M 0-0-0	7- 3-17	54	Neg.	N.	N.	7- 2-17	At.	Operated on August 5, 1918. Cancer found. Died, March, 1919.
	7105	....	.....	.....	.....	.....	.....	0 M 23-0-0 15 M 31-8-6	8-22-17	55	.....	.....	.....	8-20-17		
150	7609	Syphilis. Syphilitic neuritis.	64	M.	++	England.	0	?	....	?	Cancer.	N.	G.	11-22-17	At.	
	8772	? Pernicious anemia. Syphilis.	.....	.....	++	.....	9	0 M 2-6 16 M 20-20	6- 9-18	60	.....	.....	.....	6- 5-18	T.	Died, January, 1919.
	9166	? Pernicious anemia. ? Hodgkin's disease. Syphilis.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	8-26-18		

* Upper figure is the free HCl, lower is the total acid, expressed in c. c. of N-10 HCl per 100 c. c. stomach contents. M indicates test meal.
† Hemoglobin determinations made the same day as gastric analysis or within a few days. ‡ T = typical. S = suggestive. N = normal.
§ G = gray. W = white. N = normal. ‖ T = typical. S = suggestive. At = atypical.

Omitting these two last cases in which the diagnosis was questionable, in only one case in the 105, or 0.95 per cent, was the presence of free HCl demonstrated.

Three patients under observation showed a gastric anacidity, with a normal blood; but later all developed the typical picture of pernicious anemia. In one patient (Case 66) anacidity had been found six years before the diagnosis of pernicious anemia was made. At that time the hemoglobin was 90 per cent, and the blood smear normal. In the second patient (Case 73) a diagnosis of achylia gastrica and gastric hypermotility with normal blood, was made twenty months before the pernicious anemia became evident. In the third (Case 5) arterio-sclerosis, secondary anemia and achylia gastrica were diagnosed, three months before the pernicious anemia could be recognized. These observations indicate that the changes in the gastric contents antedate those in the blood and, together with the analyses presented, show that the anacidity is persistent here throughout the course of the pernicious anemia irrespective of the improvement in other findings so characteristic of this disease.

Of special importance is the group of cases in which the gastric analysis was essentially the determining factor which made us hesitate to make a diagnosis of pernicious anemia, and which suggested that we might be dealing with some other disease. As will be shown by a discussion of these cases, the presence of free hydrochloric acid in the gastric secretion throws doubt on the diagnosis even when all other factors point to pernicious anemia.

Special Cases

The following seven cases are included in Table I and are discussed here in detail because, although they suggested pernicious anemia in many respects, subsequent developments proved that some other condition was present and that the anemia was of a secondary type. Five of these cases demonstrate the importance of questioning the diagnosis of pernicious anemia when free hydrochloric acid is present in the gastric juice.

Case 144.—A painter, 37 years of age, was admitted August, 1913. Complaint: shortness of breath and an infected hand. The family and past history were negative. He had been subject to attacks of abdominal pain of a few days' duration, but not of sufficient severity to force him to stop work. Slight jaundice developed during these attacks. Two weeks before admission he had cut the thumb of his left hand. The wound had become infected and it was for this reason that he entered the hospital. His shortness of breath never had been very troublesome. Physical examination showed a marked brownish pigmentation of the skin, no lead line, a peculiar yellowish appearance in the scleræ, more like fat deposits than jaundice, and a markedly enlarged spleen, 10 cm. below the left costal margin. The patient had noticed that his skin had been growing darker during the past year. The urine never contained bile. The blood showed a hemoglobin of 65 per cent; erythrocytes, 2,544,000; leucocytes, 7,500. Differential: polymorphonuclears, 67 per cent; large lymphocytes, 27.5 per cent; small lymphocytes, 3.5 per cent; eosinophiles, 1.5 per cent; basophiles, 0.5 per cent. In the smear were noted marked poikilocytosis and anisocytosis, slight diffuse polychromatophilia and stippling and an occasional nucleated red cell. The color index was persistently above 1. The patient had no fever and no gastric analysis was made at this time. He was thought to have pernicious anemia. He was discharged in good health and has remained so.

In July, 1916, he was called back to the hospital. He seemed to be in the same general condition as when seen three years before. He had had no new symptoms and was working hard. At this time he had a recrudescence of a chronic gonorrhea. The hemoglobin was 74 per cent, the erythrocytes were 4,400,000, and the smear showed a slight variation in the size and shape of the erythrocytes, predominating microcytes with occasional macrocytes. The tongue was smooth and pale and the skin was markedly pigmented. No bile was present in the urine. The liver was not felt but the spleen was more than a hand's breadth below the left costal margin. Gastric analysis showed a normal quantity of free hydrochloric acid. A fragility test of the red cells was made and hemolysis was found to begin at 0.43 per cent NaCl and to be complete at 0.33 per cent; a normal control done at the same time giving 0.36 per cent and 0.25 per cent. There was, therefore, a slight increase in the fragility of the erythrocytes. To-day the patient is working and feeling well. The most probable diagnosis made by two observers was hemolytic jaundice, for certainly it would have been very unusual for a case of pernicious anemia to go for seven years with no symptoms of the disease other than the suggestive blood picture.

Case 145.—A Swedish woman, 33 years of age, entered the hospital with a history of two attacks similar to her present complaint, one eight years and the other two years before admission. She had enjoyed her customary good health between these attacks. The present upset had begun two months before, and was characterized by vomiting, weakness and increasing pallor. Physical examination showed pallor, increased pigmentation of the skin, and a systolic murmur at the base of the heart. The blood examination was typical of a primary anemia—a leucopenia, high color index, nucleated red cells and variation in size and shape of the erythrocytes. The Wassermann test was negative. She had some fever and the heart rate was accelerated. The gastric analysis showed complete anacidity. The presence of fish tapeworm eggs was discovered, and, as a result of treatment, four complete dibothriocephalus latus parasites were passed. The patient made a complete recovery both symptomatically and as far as her blood picture was concerned, and remained perfectly well for the two years during which we were in touch with her. When seen ten months after her admission to the hospital, the hemoglobin was 124 per cent (Sahli), but the gastric juice still showed anacidity.

Case 146.—A boy, 17 years of age, entered the hospital December 4, 1915, stating that eight weeks previously his parents noticed that he was growing pale. Two weeks later he began to feel weak, lost his appetite and was often nauseated and vomited. Three weeks before admission he stopped work on account of weakness, dyspnea, dizziness and headache. He did not have any pain, but often felt cold and chilly. Physical examination showed marked pallor, a slightly enlarged heart with a loud systolic murmur over the precordium. The edge of the spleen was felt 2 cm. below the left costal margin. The blood picture was typical of pernicious anemia. The hemoglobin was 37 per cent; erythrocytes, 1,304,000; leucocytes, 6,400, and the stained smear showed nucleated cells, macrocytes, microcytes, granular and diffuse polychromatophilia. Three gastric analyses done during his stay in the hospital all showed complete anacidity. The Wassermann test and blood cultures were negative. He ran a fever over 100° most of the time with a heart rate of about 100. He gradually improved without medication and, when discharged, the blood and physical examinations were normal. As a mechanic's helper in a garage, the patient had been exposed to exhaust fumes, and although most of the important features of the case pointed to the diagnosis of primary anemia, this was doubtful, and he was discharged with a diagnosis of questionable pernicious anemia, or anemia secondary to occupation. This patient, when seen ten months later, seemed to be in perfect health. He had changed his occupation. His hemoglobin then was 119 per cent and he had 6,136,000 erythrocytes per cubic millimeter. At this time the gastric analysis did not show a persistent anacidity, for in the second sample after the test breakfast the free hydrochloric was 12. He has remained well for five years and has been working all the time. In the light of the progress of this case, pernicious anemia can be safely ruled out, and it is interesting to note that this patient in whose case all the findings pointed to pernicious anemia should have begun, on recovery, to show free hydrochloric acid in the gastric juice, in contrast with patients suffering from a true pernicious anemia.

Case 147.—A married woman, 62 years of age, entered the hospital February 28, 1917. For one year she had been complaining of nausea and gas in the stomach, not particularly related to meals or effort. These symptoms had steadily grown more pronounced and she had lost some weight and strength. She had never had any pain or vomiting. Physical examination showed marked pallor of the skin and mucous membranes, with a slight suggestion of a lemon tint. The tongue was not smooth. There was very little else of a definite nature made out except for a suspicious mass in the center of the abdomen. The x-ray examination of the gastro-intestinal tract was negative except for a low position of the stomach. The blood examination showed: hemoglobin, 40 per cent; erythrocytes, 1,730,000; leucocytes, 4,300. Differential: polymorphonuclears, 74 per cent; large lymphocytes, 23 per cent; small lymphocytes, 1 per cent; eosinophiles, 2 per cent; basophiles, 0. There was slight variation in the

size and shape of the erythrocytes, but otherwise nothing remarkable. A phenolsulphonephthalein test, done twice, showed 0 per cent in two hours. Gastric analysis showed an absence of free hydrochloric in all specimens except the last in which it was 8. After being in the hospital for twelve days, she had a convulsion, followed later by periods of delirium. She improved, but then developed signs of an acute pericarditis. She finally died with signs of either compression or consolidation of the left lower lobe of the lung. Clinically, the case was considered to be one of chronic nephritis and uremia, chronic peritonitis, acute pericarditis and possibly pernicious anemia. The autopsy failed to show any evidence of pernicious anemia. There was acute pericarditis, pleuritis and peritonitis, chronic vascular nephritis and chronic cholecystitis. This case is reported in detail because the presence of free HCl in the gastric juice was enough to throw a doubt on the diagnosis of pernicious anemia, although the blood findings and general appearance of the patient were strongly in favor of that diagnosis.

CASE 148.—A school teacher, 45 years of age, entered the hospital complaining of general weakness, sore mouth, and vaginal pain. For a period of about seven or eight years, up to five years before admission, she had had symptoms of tuberculosis, cough, bloody sputum, night-sweats and fever. While in Mexico for her health five years before, she had had symptoms similar to her present illness. For three months she was greatly troubled with pain and burning of her tongue. She also had similar sensations in the vagina. She lost strength. Her condition repeatedly improved for a few days and then she relapsed. Physical examination showed a reddened, tender tongue and small hæmorrhagic punctate areas on the mucous membrane of the mouth. There were also signs of consolidation at the apex of the left lung. The general physical examination was not otherwise particularly significant. The urinary findings suggested the possibility of renal tuberculosis. Gastric analysis showed a persistent absence of free HCl in all specimens. The blood gave: hemoglobin, 78 per cent; erythrocytes, 2,748,000; leucocytes, 7,500. Differential: polymorphonuclears, 63 per cent; large lymphocytes, 32 per cent; small lymphocytes, 2 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent. There were many macrocytes and microcytes, but no nucleated cells. The temperature rose in the evening to just above 99° most of the time and the pulse was around 80. At this time, although sprue was considered, the condition was regarded as pulmonary tuberculosis, possible renal tuberculosis and a possible pernicious anemia. She returned to the hospital five months later, complaining of cramp-like pains in the abdomen and diarrhœa with blood and mucus in the stools. It was now thought that she had sprue in addition to the pulmonary tuberculosis. She left the hospital improved, but died about six months later. An autopsy showed tuberculosis of the lungs, left kidney, bladder, and large intestine. (Dr. A. W. Sellards thought that a diagnosis of sprue should be added.) This case is included as one in which there were many features pointing to pernicious anemia but in which generalized tuberculosis or sprue was the underlying factor. Recently Wood[3] has called our attention to the frequency of blood changes in sprue similar to those of pernicious anemia. Possibly in some of these patients the gastric content will show the presence of free HCl, and then pernicious anemia can be ruled out, but in the case just cited there was complete anacidity.

CASE 149.—A trained nurse, 42 years of age, complained of increasing weakness, dyspnea and palpitation of the heart. Twelve years previously she had had an attack of acute pain in the right lower quadrant, diagnosed as acute appendicitis. Three months before admission there had been a recurrence of acute pain in the right lower quadrant and on three occasions bloody stools had been passed. Physical examination showed a well-nourished, middle-aged woman with marked anemia and a lemon tint to the skin. A loud systolic murmur could be heard over the precordium, and a large mass was felt in the region of the cæcum. The tongue was not smooth. The blood showed: hemoglobin, 54 per cent; erythrocytes, 3,528,000; leucocytes, 7,500. In the stained smear were noted a moderate amount of anisocytosis and poikilocytosis, considerable achromia, and two nucleated red cells. The gastric analysis showed an absence of free HCl in the fasting content, but a free HCl of 23 in the first sample after the test breakfast. Although the x-ray of the gastro-intestinal tract was negative, the case was diagnosed: pernicious anemia (?) and carcinoma of the cæcum (?). She was discharged unimproved, and it was learned that a year later a malignant tumor of the abdomen was discovered at operation and she subsequently died. Here, again, we have a case that suggested pernicious anemia in some respects, but which showed free HCl in the gastric contents. Later on it was proved that the anemia was due to carcinoma of the cæcum.

CASE 150.—A Hebrew, 67 years of age, entered the hospital complaining of pain in the left hip of three months' duration. His past history and family history were unimportant. His present trouble had begun with pain in the hip extending down to the ankle, and difficulty in lifting his foot. Some days later pain had appeared in the left shoulder and elbow. These pains had kept on recurring and growing more intense so that he had had to stop work and could not sleep; they had become shooting in character and extended to both arms and legs. He had had fever and severe chills and had lost some weight. Physical examination showed peripheral arteriosclerosis. The heart was normal except for a loud systolic murmur all over the precordium. The inguinal glands were enlarged and an old scar was present on the penis. There was a definite Romberg's sign with increased deep reflexes of the legs. No Babinski or clonus. There was considerable tenderness on pressure over the nerve trunks of the legs and arms. The extensor surfaces of the arms and hands were abnormally pigmented. The Wassermann reaction was double plus. The patient ran an irregular fever, 100-102°, with a pulse rate between 70 and 90. He was in the hospital on three different occasions, improving each time, first under anti-luetic treatment and later after transfusions. The blood showed: hemoglobin, 60 per cent; erythrocytes, 2,776,000; leucocytes, 11,900. Differential: polymorphonuclears, 73 per cent; lymphocytes, 9 per cent; transitionals, 14 per cent; eosinophiles, 4 per cent. There was variation in size and shape of the erythrocytes, some macrocytes, and an occasional nucleated red corpuscle. The diagnosis was not certain, but the case was considered as one of pernicious anemia and syphilis. A gastric analysis showed a slight amount of free HCl in the first two samples of the test breakfast, the figures being 2 and 6. We considered this to be sufficient to throw considerable doubt on the diagnosis of pernicious anemia. Subsequently, an inguinal gland was excised and the pathologist reported a lymphoblastoma of the Hodgkin's type. The patient died about 14 months after his first admission to the hospital.

The above seven cases gave evidence in the general history, physical examination, or the blood findings, suggesting a more or less positive diagnosis of pernicious anemia, although the final outcome made it unlikely that pernicious anemia had anything to do with the condition. One of these seven patients turned out to have a dibothriocephalus latus infection and was apparently cured after this had been treated. She had absolute anacidity on two different occasions. Another was found to have sprue and tuberculosis of the lungs, kidney, bladder and intestines. This patient also showed gastric anacidity on two different occasions. In all the other five the stomach contents showed some free HCl. One was probably a case of hemolytic jaundice, a second was an atypical type of secondary anemia resulting from toxic fumes to which the patient had been exposed in his work; the third was a case of chronic nephritis and cholecystitis with terminal acute pericarditis, pleuritis and peritonitis; the fourth was cancer

of the cæcum, and the last was Hodgkin's disease and syphilis. We feel from the evidence in this group of cases that if any free hydrochloric acid is found in the gastric contents one should seriously question the diagnosis of pernicious anemia. Conversely, absence of free hydrochloric acid suggests the possibility of pernicious anemia and other features of the disease should be carefully sought.

The Incidence of a Family History of Anemia

Bartlett[4] gives an account of a family of eight in Vermont, father, mother, five sons and one daughter. The father died at 44 of anemia with symptoms of pernicious anemia. There was no blood examination, and the autopsy failed to show the cause of death. The mother died at 60 of anemia, but there was no autopsy or blood examination. One son died at 24 of anemia with symptoms of pernicious anemia. There was no blood examination but autopsy showed findings typical of pernicious anemia. A second and third son died at 35 of typical primary anemia, confirmed by autopsy and blood examinations. A daughter was alive at 49, with a marked chlorosis, having a hemoglobin of 40 per cent and 5,000,000 red cells. All these people lived on the same farm and the only two sons who did not have anemia lived elsewhere most of the time.

With the above facts in mind the family history of all our cases of pernicious anemia has been carefully studied, and appreciating that cases of pernicious anemia, when incorrectly diagnosed, are apt to be ascribed either to cancer or tuberculosis, the incidence of these two diseases as well as that of anemia was determined. Of the 143 cases, in 41 there was a definite family history of cancer or tuberculosis or both. (In the family history are included sisters and brothers, the parents and children.) In nine cases it was possible to obtain a definite history of pernicious anemia in other members of the family, of whom six have died. In two there was a history of members of the family dying of anemia, but it was not known whether the anemia was of the pernicious type or not, and in 91 cases the history was negative. There was a frequent familial occurrence of cancer and tuberculosis among these patients. Probably some cases of true primary anemia are included because of the difficulty in differential diagnosis in general practice. Considering that 6.3 per cent of these patients have a positive family history of pernicious anemia, we are impressed by the fact that there is an important familial factor in this disease, but whether this factor is one of heredity or one of environment our analysis does not reveal.

Racial Discrepancies in the Prevalence of Pernicious Anemia

Upon this point there are differences in opinion and since there is not sufficient evidence as yet to support definite conclusions, an analysis of the present series of cases may be to the point.

Cabot[5] in his exhaustive review of pernicious anemia, in discussing etiological factors, states: ". . . . Race, civil condition, residence, do not seem to have any special bearing."

TABLE 2*

	All countries	Born in U. S.	Total foreigners	Russia	Canada	Ireland	England	Italy	Sweden	Denmark	Germany	Greece	Miscellaneous	All foreign countries except Ireland, England, Sweden and Denmark
Total admissions to hospital.	23323	13696	9627	2193	2070	1813	795	668	278	37	358	323	1092	4634
Per cent admissions to hospital.	100	58.7	41.3	9.4	8.9	7.8	3.4	2.9	1.2	0.2	1.5	1.4	4.7	19.9
Total P. A. cases.....	143	86	57	3	23	11	8	1	6	2	1	0	2	7
Per cent P. A. cases.....	100	60.1	39.9	2.1	16.1	7.7	5.6	0.7	4.2	1.4	0.7	0	1.4	4.9
Per cent of all admissions born in various countries having P. A.	0.61	0.63	0.59	0.14	1.11	0.61	1.01	0.15	2.16	5.4	0.28	0	0.18	0.15

* These figures include all admissions to hospital to January 1, 1921.

Silberman[10] made an extensive study of the occurrence of pernicious anemia in East Prussia and concludes that locality has something to do with the occurrence of the disease among certain races. Although statistically definite conclusions from the figures here given are not warranted, the following suggestive figures are interesting:

We have used two ways of determining the influence of such factors in this series: First, we have compared the percentage of the total number of admissions to the hospital from a given country with the percentage of the total number of pernicious anemia cases in persons born in that country (see 2d and 4th lines of Table 2). Thus, 9.4 per cent of all medical admissions came from Russia, but only 2.1 per cent of the cases of pernicious anemia are Russian immigrants. Contrast the Canadians—whereas 8.9 per cent of all admissions came from Canada, yet 16.1 per cent of the pernicious anemia cases were in Canadians. In these two countries the total number of admissions is sufficiently large to give these statistics some value. There were 2193 Russians and 2070 Canadians admitted, but only 3 Russians with pernicious anemia as compared with 23 Canadians. We feel that it is not possible to ascribe

this striking difference merely to chance. A similar discrepancy arises in comparing Sweden and Italy. There were two and one-half times as many Italians as Swedes admitted, but there was only one Italian with pernicious anemia, whereas there were six Swedes.

This will be made clearer by reference to the last column of Table 2, in which admissions from foreign countries are tabulated, excluding those in which the disease seems to be more prevalent, i. e., Canada, Ireland, England, Sweden and Denmark. There were 4634 admissions or 19.9 per cent of our cases from the foreign countries not so excluded, yet there were only 7 or 4.9 per cent cases of pernicious anemia from these other countries. This suggests that the disease is about one-fourth as prevalent among Eastern Europeans as among citizens of the United States and the five foreign countries mentioned above.

The second basis of comparison is the ratio of the number of patients with pernicious anemia born in a given country to the total number of admissions to the hospital for all causes from that country (Table 2, line 5). For example, 0.61 per cent of all patients admitted to the hospital have pernicious anemia, but over 1 per cent of all patients from Canada and England and over 2 per cent of those from Sweden had the disease, in contrast to only 0.14 per cent and 0.15 per cent of those from Russia and Italy respectively. The foreign countries charted in the last column of Table 2 show a low incidence of the disease, only 0.15 per cent, or about one fourth the general admission rate. Inasmuch as almost all our Jewish patients of middle or advanced age have been born in Russia, and we have a fairly large percentage of Jewish admissions, the infrequency of the disease in Russian-born patients bears out the clinical impression that the disease is comparatively infrequent in the Jewish race. Similar tables from other hospitals accumulating a large statistical basis will be necessary before the evidence for these racial discrepancies is conclusive, but it is certainly suggestive from this small group that pernicious anemia is more frequent in Americans and immigrants from Canada, England, Ireland, Sweden and Denmark than in those from Russia and Italy and eastern Europe.

SYPHILIS AND PERNICIOUS ANEMIA

It is known that syphilis may occasionally produce a rather severe degree of anemia which may sometimes present a blood picture that can readily be compared with that of pernicious anemia. With this in mind, an analysis was made of the incidence of a positive Wassermann reaction in the blood of all the cases studied. In two of the 143 cases a Wassermann test was not made and of the remaining 141, all were negative except six, *i. e.*, 4.3 per cent were positive. Inasmuch as the average incidence of a positive Wassermann reaction in all medical admissions to this hospital is about 12 per cent[6] we can readily see that the incidence among these cases is one third of the average. Of these six positive cases, there was a definite past history of a hard chancre in but one. Three of the patients died within 29, 16 and 12 months, respectively, after their admission, despite intravenous treatment for syphilis. Each presented the findings typical of pernicious anemia in the blood and gastric contents and on general physical examination. Of the other three patients who gave positive Wassermann reactions one has done quite well for four and one-half years after receiving three intravenous injections of salvarsan. Another has been doing pretty well for three years following three intravenous treatments with salvarsan, and the last one left the hospital six months ago, after receiving a similar course of treatment. These patients also gave quite a typical clinical picture of a primary anemia.

From the above data the conclusion is warranted that in our cases, syphilis has borne very little relation to the development of pernicious anemia. Furthermore, when the blood of a patient presenting findings of pernicious anemia has given a positive Wassermann reaction, the course of the disease has not been changed and antisyphilitic treatment has had no effect upon it. (The two patients who have done well for four years and seven months and three years, respectively, will have to be followed for a much longer time before they can be used as evidence against this statement.)

THE FREQUENT OCCURRENCE OF EOSINOPHILIA

In a study of 110 cases by Cabot[7] it was found that an eosinophilia of over 4 per cent was found in 13 per cent of the cases on the first blood examination. The occasional occurrence of marked eosinophilia has also been observed in pernicious anemia. Beifeld and Barnes[8] reported a case of severe anemia with eosinophilia ranging between 9 per cent and 53 per cent. The case was fairly typical of pernicious anemia in other respects, but the high eosinophilia led them to consider this as a remote probability.

In the cases here reported frequent blood examinations were made and the occurrence of more than the usual percentage of eosinophilic leucocytes was very striking. It must be borne in mind that the following figures include some patients who on one or two occasions only showed the increase in these cells, although many had a more persistent eosinophilia. Of the 143 patients studied (see Table 3), 89 never showed more

TABLE 3

Eosinophiles ..	0–4%	5–9%	10–14%	15–19%	20–24%	25–30%	Total
No. of cases...	89	43	5	4	1	1	143
Per cent.....	62.2	30.1	3.5	2.8	0.7	0.7	100

than 4 per cent of eosinophiles; of the 43 patients who showed 5-9 per cent eosinophiles, 12 had 5 per cent, five had from 10-14 per cent, four from 15-19 per cent, one from 20-24 per cent and one had 28 per cent of eosinophiles. In other words, 54 patients (37.8 per cent) had 5 per cent or more of eosinophiles and 29.4 per cent had 6 per cent to 28 per cent of eosinophiles.

The significance of the above figures is that a high eosinophile count need not militate against the diagnosis of perni-

cious anemia, although the stools show no evidence of parasites. In one patient with the typical clinical and blood picture of pernicious anemia, dibothriocephalus latus eggs were found and four complete worms were expelled, but her blood showed only 8 per cent eosinphiles.

"The Typical Blood Picture"

An attempt was made to determine the frequency of typical blood findings in the disease, taking into consideration the presence of macrocytes and deeply stained red cells, the high color index, the low white blood cell count, the appearance of nucleated erythrocytes, and the variation in the size, shape and staining qualities of the red blood cells. The decision as to whether a blood finding is typical, suggestive or atypical of pernicious anemia is an arbitrary one and of course might well differ in the opinion of different observers. However, at a hospital where considerable interest is manifested in blood diseases and where a fairly large number of cases of anemia are seen, the general impression does not differ much from the average opinion in other clinics. Of the 143 cases, the blood examination was considered typical in 110, or 76.9 per cent, suggestive in 26 or 18.2 per cent and atypical or within normal limits in 7, or 4.9 per cent. The fact that about 23 per cent did not have the blood typical of the disease is of importance in relation to the much rarer findings of free hydrochloric acid discussed above. In fact a blood picture typical of pernicious anemia may be present in other diseases and in such cases the gastric analysis becomes an important help in making the proper diagnosis.

Unnecessary Abdominal Operations in Pernicious Anemia

It is not infrequently found that patients suffering from pernicious anemia have been operated on previously for the same complaints that eventually bring them to a medical clinic. There were six such patients out of 125 in this series

TABLE 4

Case number. See Table 1	Operation	Interval between operation and admission	Result
Case 1....	Gastric ulcer.....	2 years...	None found.
Case 30....	Gastric ulcer.....	11 years...	None found.
Case 79....	Gastric ulcer.....	4 months.	None found.
Case 103....	Gastric cancer	19 months.	None found.
Case 136....	Gall-stones	4 years...	None found.
Case 94....	Chronic cholecystitis...	6 years...	Symptoms persisted.

who were definitely questioned concerning any previous operation. Three had been operated upon for gastric ulcer and one for gastric cancer, but no such lesion had been found. Two had been operated upon for gall-bladder disease, but the same symptoms had persisted after operation. In these six cases operative procedures had been fruitless, although it is quite well known that patients with pernicious anemia occasionally come to autopsy showing either gall-stones or chronic cholecystitis. However, it is very unlikely that the abdominal symptoms of pernicious anemia are relieved by surgical intervention and some of these operations might have been prevented by more careful medical study of the case.

The Appearance of the Tongue

The appearance of the tongue is generally considered to be of distinct aid in diagnosis. "Typically" the tongue is smooth, glistening and pale, the papillæ are atrophic, especially around the edges. Wallgren [9] has carefully studied these tongue changes. With these criteria the appearance was described as typical of pernicious anemia, suggestive, or within the normal limits. Of the 143 cases, notes on the tongue, made in 127, describe it in 82, or 64.4 per cent, as typical; in 24, or 18.9 per cent, as suggestive, and in 21, or 16.5 per cent, as within normal limits. In more than half the patients, therefore, the tongue is typical in appearance. The simplicity of the observation gives it great value in suggesting the disease and in selecting those patients who should have more careful study.

The Occurrence of Prematurely Gray Hair

In observing large numbers of patients suffering from pernicious anemia, the clinician is impressed with the great prevalence of gray hair. In fact, he is often struck by its beautiful white, silky appearance. Of course, it is evident that a large number of adults might well have gray hair, and as the average age incidence of this disease is about fifty years, it is not surprising that the hair is frequently found to be gray or white. Notwithstanding this, however, it seems fair to say that patients with pernicious anemia are prone to have gray hair and even white hair prematurely; in fact, a fair number of the comparatively younger cases show it. A note as to the color of the hair was made in 119 of the 143 cases. Considering the cases under fifty years of age, we find the following:

Of 4 cases in the 3d decade, 50 per cent had gray or white hair
Of 12 cases in the 4th decade, 33 per cent had gray or white hair
Of 37 cases in the 5th decade, 78 per cent had gray or white hair

Sex Incidence

There is some difference of opinion as to whether pernicious anemia is more frequent in males or females. Cabot thought that the statistics, according to which females predominated, must have included cases of anemia associated with pregnancy and which were, therefore, not true primary anemias. Osler [10] stated that the disease was more common among males. Colquhoun [11] in discussing pernicious anemia in New Zealand states that in fifteen years, in the whole of New Zealand, 1078 persons were reported as having died from anemia, of whom 537 were males and 541 females.

In this series of 143 cases, there were 59 males and 84 females (Table 5). Cases of anemia associated with preg-

nancy were observed in the hospital, but these were not diagnosed as pernicious anemia. The proportion, therefore, in the sexes is about as two to three, with the females predominating.

PROGNOSIS

In following these patients to determine the end results as far as was possible, it was learned that 97 had died, of whom 48 were males and 49 females. The average age of the 48 males who died was 51.6 years and that of the 49 females was 50.9 years. Thirteen were discharged from the hospital within six months of the time this study was closed and no information concerning their condition was obtained. Thirteen could not be traced and 21 were alive. Of these 21 living patients six have lived more than four years after their first admission to the hospital.

TABLE 5

	Number of cases	Number of males	Average age	Number of females	Average age*
All P. A. cases....	143	59	51.7	84	50.4
Those dead.....	97	48	51.6	49	50.9
Autopsies	18	10	45.6	8	54.8

*All ages are those obtained on the first admission to the hospital.

The average age of the entire group on their first admission was 50.8 years. The average age of the 59 males was 51.7 and that of the females was 50.4 years. In regard to the predominance of females mentioned above, it would seem that if cases of pregnancy were included in these statistics the average age of the females would be considerably lower, for there were 25 more females than males and these 25 cases, if in any way associated with pregnancy, would have diminished the age of this group to an appreciably lower level than 50 years.

It is important to bear in mind that, at least in New England, pernicious anemia is not a rare disease and that in a hospital service probably more cases are seen than in the average outside practice because of the obscurity of the condition and the difficulty in diagnosis. However, during the period covered by this series of cases, 105 cases of typhoid fever and 401 cases of lobar pneumonia as against 143 of pernicious anemia were observed. The general course of the disease is very similar to that of cancer, *i. e.*, the overwhelming majority of the patients die within a few years, while a small proportion have remissions of considerable duration, as much as four or more years.

SUMMARY

Our study of 150 cases of pernicious anemia includes seven patients in whom the subsequent course of the disease either indicated that the diagnosis was wrong or threw considerable doubt on its correctness. The gastric secretion in the fasting contents and after an Ewald test breakfast was analyzed in 107 of the 143 cases of pernicious anemia. Analyses were made repeatedly on the same patient in many instances when the blood condition was low and when normal, and some analyses extended over many years. In only three cases was free HCl found at any time in the gastric secretion, and in two of these cases the diagnosis of pernicious anemia was questioned. These figures, then, show a persistent anacidity in 104 or 99 per cent of cases of pernicious anemia. Pepsin was tested for in a small number of cases and was always found lacking.

Evidence has been brought forward that the changes in the gastric secretion occur very early in the disease, often years before the blood picture develops, and that once established they are never altered by the remissions so characteristic of the disease. The presence of free HCl in a suspected case of pernicious anemia is important evidence against this diagnosis. In five such patients who showed varying amounts of free HCl in the gastric secretion, operation, post-mortem examination, or subsequent findings practically ruled out pernicious anemia. Its absence should suggest pernicious anemia as a probable diagnosis worthy of careful consideration.

A distinct familial incidence was discovered in studying these 143 cases. In nine patients there was a definite family history of pernicious anemia in some other member of the family. In two others there was a history of death from an unknown type of anemia. Forty-one had a family history of tuberculosis or cancer or of both, and as these diseases are easily confused with pernicious anemia, these figures may well include cases of anemia.

There are racial discrepancies in the incidence of this disease. The figures studied would indicate that pernicious anemia is less frequent in the Italians, Russian Jews, and immigrants from Eastern Europe, than in Americans, Canadians, or immigrants from Ireland, England, Sweden or Denmark.

Syphilis bore no relation to the development or course of pernicious anemia in this series. Of 143 patients, six, 4.3 per cent, gave a positive Wassermann, which is about one-third the percentage of positive Wassermann reactions in all medical patients admitted to the hospital. When the Wassermann reaction was positive, anti-luetic treatment did not alter the course of the anemia.

The presence of eosinophilia is a common finding in pernicious anemia. Out of the 143 patients, 54 showed 5 per cent or more at one time or another. Even a very high eosinophilia—25 per cent or more—is not incompatible with the disease.

In 76.9 per cent of the cases the blood smear might be called typical of pernicious anemia, in 18.2 per cent it was suggestive and in 4.9 per cent it was atypical or within normal limits. This is in striking contrast with the more constant finding of anacidity.

Six of our patients had undergone previous abdominal operations for the symptoms similar to those that brought them into the hospital. Three of the operations were for gastric ulcer, one for gastric cancer, one for gall-stones, and one for chronic cholecystitis.

It was found that of 127 patients in whom the appearance of the tongue was described, in 63.8 per cent it was typically

smooth and atrophic, in 19.7 per cent it was suggestive, and in 16.5 per cent its appearance was about normal.

Notwithstanding the fact that this disease belongs to adult age, the hair seems to turn gray prematurely and often takes on a strikingly silky-white appearance.

The proportion of males to females in this series was as two to three with the females predominating. An analysis of the ages of these patients shows that the type of anemia associated with pregnancy which may be confused with pernicious anemia has not been included in these figures. The average age of all patients, of the males and females taken separately, and of those that have died is approximately the same—about 51 years.

Conclusions

Persistent absence of free HCl is practically a constant finding in cases of pernicious anemia. In our series it was noted in 99 per cent of the cases. It is often present years before the blood shows any of the typical changes, and possibly always antedates them. It is, therefore, of considerable importance in diagnosis.

There seems to be a distinct familial factor in pernicious anemia.

The incidence of this disease in English speaking people and Scandinavians was greater than in immigrants from Russia, Italy and Eastern Europe.

Syphilis played no significant rôle in this series.

Eosinophilia, even of a very marked degree, was a frequent finding.

The proportion of males to females was as 2 to 3. The average age of both sexes was about 51 years.

BIBLIOGRAPHY

1. Faber, K.: Anaemische Zustände bei der Chronische Achylia Gastrica. Berl. klin. Wchnschr., 1913, Nr. 1, p. 958.

2. Friedenwald, J., and T. H. Morrison: Gastro-intestinal Disturbances in Pernicious Anemia. Jour. Am. Med. Assn., 1919, LXXIII, 407.

3. Wood, E. J.: The Recognition of Tropical Sprue in the United States. Jour. Am. Med. Assn., 1919, LXXIII, 165.

4. Bartlett, C. J.: Family Pernicious Anemia, with Report of Cases. Jour. Am. Med. Assn., 1913, LX, 176.

5. Cabot, R. C.: Osler and McCrae's Modern Medicine, 1915, IV, 819.

6. Walker, I. C., and D. A. Haller: Routine Wassermann Examination of 4000 Hospital Patients. Jour. Am. Med. Assn., 1916, LXVI, 488.

7. Cabot, R. C.: Pernicious Anemia: A Study of One Hundred and Ten Cases. Am. Jour. Med. Sc., 1900, LXX, 139.

8. Beifeld, A. F., and M. E. Barnes: Severe Anemia with Eosinophilia. Johns Hopkins Hosp. Bull., 1916, XXVI, 181.

9. Wallgren, I.: Om forandringarna i tungan vid den perniciösa anemien, särskildt i histologiskt afseende. Finska läk.-sällsk. handl: 1919, 61, 828-58.

10. Osler's Practice of Medicine, 1905, p. 724.

11. Colquhoun, D.: Pernicious Anæmia. New Zealand Med. Jour., 1918, 57, 126.

12. Silberman, S.: Über die geographische Verbreitung der Leukämie und der perniziösen Anämie in Ostpreussen. Med. Klin., 1920, 16, 183.

GLAND PUNCTURE AS A DIAGNOSTIC MEASURE

By C. G. Guthrie

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

My attention was first directed to the possibilities of gland puncture as a diagnostic measure through the study of an imported case of human trypanosomiasis in 1912.[1] The patient had contracted the infection in the Belgian Congo three and a half years earlier and, after a rather characteristic course, the progress of the disease was arrested by injections of atoxyl. He was warned that he was not cured and would certainly have a relapse unless treatment was continued, but being free from symptoms he came to this country and remained apparently well until five weeks before he came under our observation. When we saw him, symptoms had returned but physical examination was negative except for a palpable spleen and general glandular enlargement. Repeated examinations of his blood and spinal fluid, both direct and after various methods of concentration, were negative for trypanosomes, and inoculation of susceptible animals with blood and spinal fluid failed to produce infection. Aspiration of an enlarged cervical gland with a syringe and small needle, however, yielded one or two drops of fluid in which was found one motile trypanosome. This finding was confirmed by the removal of a gland which was used for intraperitoneal inoculations of six white rats; all developed trypanosomiasis from which they eventually died.

Diagnosis by gland puncture was not a new method in trypanosomiasis, but had been recommended by Grieg and Gray[2] in 1904, and used with success by various workers in the sleeping sickness regions of Africa. It has also been used for the recovery of the etiological agent in syphilis,[3] in bubonic plague,[4] in filariasis[5] and in East Coast fever of cattle.[6] Although no reference to the use of this procedure in Leishmaniasis can be cited, the report by Cochran[7] of finding Leishmania by examination of excised cervical glands indicates that the simpler method would probably be successful in this disease also. A similar prediction might be made concerning yaws and leprosy, diseases in which there is often glandular enlargement and in which the causative organisms have been demonstrated in the glands.[8] In 1907, White and Proscher[9] announced the discovery of spirochætes in juice aspirated from the lymph glands of (1) a patient with acute lymphatic leukemia, (2) a patient with Hodgkin's disease, and (3) a guinea-pig previously inoculated with gland material from a case of lymphosarcoma. These findings lack confirma-

tion and various competent observers to whom the specimens were submitted expressed the belief that the spirochæte-like bodies seen were actually reticulum fibrils.[10]

Although a valuable aid in diagnosis, gland puncture had thus far been used only for the recognition of various etiological agents of disease, bacteria, protozoa and filariæ. It seemed possible that the method might be applied to the study of other conditions by the recovery of cellular material for microscopic examination. A few attempts were made in 1917 but no considerable series of cases was secured until 1920-1921. Even yet the series is too small, particularly the number of cases in some of the diseases studied, to permit of sweeping conclusions as to the value of the method. The results have seemed sufficiently promising, however, to warrant a brief report.

Method

In selecting a gland for puncture three requirements are essential. (1) The gland must be of a size sufficient to permit aspiration; tiny shot-like glands are not suitable for this purpose. (2) The location of the gland should be such as to render firm fixation possible and (3) injury of important structures improbable. By observing these points it has been possible in each instance to secure material from the gland and to avoid trauma of surrounding organs.

For the puncture a 2 c. c. Record syringe is used, equipped with a 21-gauge needle, 5 cm. in length. The point of the needle has a short bevel and is sharpened each time just before sterilization. After boiling needle and syringe, sterile salt solution is drawn into the syringe and then carefully removed, the syringe being held vertically with the needle downward, and the plunger moved in and out several times to expel all excess of fluid.

The skin over the gland selected for puncture is painted with iodine followed by alcohol. The gland is then firmly fixed by the fingers of an assistant, care being taken to have the skin over the gland stretched tightly; when fixation is satisfactory, the area to be stuck is again painted with iodine.

Before performing the puncture the plunger is pushed as far in as it will go and the syringe is held perpendicular to the skin. As the needle enters the gland, the sensation imparted to the person holding the syringe,while difficult to describe, is characteristic and unmistakable. The needle is inserted well into the gland, approximately half way through it. The syringe and needle are then rotated once about their longitudinal axis and the plunger is drawn out to the 1 c. c. mark to produce suction. The needle is then slowly withdrawn, negative pressure being maintained throughout or even increased by drawing the plunger back somewhat further. When the needle is completely withdrawn, there is heard a rush of air into the syringe through the needle, but only rarely is anything to be observed in the barrel of the syringe, at most only a drop or two of milky fluid. At first glance the results seem quite disappointing and it may appear that no material whatever has been obtained. In no instance, however, have I failed to secure some material, although from very firm, fibrotic glands the amount obtained may be very scanty. Ordinarily one secures enough to make two or three fresh preparations for dark-field examination and from six to twelve dried films for staining.

After the puncture the syringe is held either at an angle of 45°, the point of the needle almost touching the surface of a clean glass cover-slip, or vertically above the cover-slip. The plunger of the syringe is then pushed in, at first slowly, or if this is not productive of results, it is withdrawn and pushed in more sharply; by this means there is expelled a tiny drop of fluid. It has been our custom to use the first two or three drops to make fresh preparations for dark-field examination and the subsequent drops for pulling cover-glass films as in blood work. Some of these films are stained with a Romanowsky stain (Wilson's modification), others by the Ziehl-Neelsen method for acid-fast organisms, and if spirochætes are found on dark-field examination, one or two films are stained in a manner designed to give permanent preparations of these organisms. Other and special stains such as the Ehrlich triacid or the oxidase stain are applied if they are indicated by the results obtained with the Romanowsky stain.

An effort has been made to consider these gland puncture preparations objectively, to secure whatever information they presented and to try to arrive at a conclusion independently of knowledge from other sources. The findings obtained by this procedure have been checked, whenever possible, by examination of direct smear preparations and stained sections from the excised gland. Of assistance also in the luetic cases has been the Wassermann reaction and the presence of obvious signs of lues, while in the other cases, a study of the blood, the physical examination of the patient and the clinical course of the disease have been of great help in checking up the results of gland puncture.

Results

Thus far there has been an opportunity to apply this method of diagnosis in cases of syphilis, tuberculosis, Hodgkin's disease, acute and chronic lymphoid leukemia, acute and chronic myeloid leukemia, simple adenitis and in one instance each of trypanosomiasis and of metastasis of malignant disease.

A positive diagnosis dependent upon the recovery of the etiological agent of the disease was possible in a number of the cases.

As was mentioned above, the finding of trypanosomes established the diagnosis in our patient with African sleeping sickness.

Actively motile treponemata were found in a goodly percentage of the luetic cases, particularly from punctures of the inguinal glands in the late primary or early secondary stage of the disease. The relatively high incidence of positive results is to be attributed largely to the selection of favorable cases, but in the main the findings agree closely with those reported by others.[8]

Acid-fast organisms, morphologically indistinguishable from tubercle bacilli, were occasionally found in material aspirated from glands clinically tuberculous and later shown to be tuberculous by histological examination. They were

found once in a caseous gland and twice in glands which were completely broken down inside but which felt firm owing to the distention of the gland capsule by the contained pus. When pus was obtained, the syringe was filled and the aspirated material treated with antiformin. From glands which were neither caseous nor broken down, tubercle bacilli were not recovered.

Streptococci and staphylococci have been demonstrated in stained preparations from aspirated glands, but in the particular instances in which they were seen, unfortunately no tubes were inoculated so I cannot report having grown these organisms from material obtained by gland puncture. Streptococci were seen in one instance of subacute adenitis and were subsequently grown from the excised gland. Clumps of staphylococci were seen in the pus aspirated from a broken down tuberculous gland, evidently a secondary infection.

The results obtained from the study of the cellular material aspirated from glands are perhaps more interesting.

In Hodgkin's disease it has been possible to make a definite diagnosis in all of the cases examined thus far. The presence of eosinophiles, large endothelial cells and the peculiar multinucleated giant cells—the so-called "Dorothy Reed cells"—gives a characteristic and usually unmistakable picture.

In the cases of leukemia the gland picture has, to a remarkable degree, reflected the blood picture; such immature forms as were to be seen in the blood were also found among the cells from the gland, and hence, little information was added by the study of the material obtained on puncture. It is possible, however, that if the blood were in an aleukemic stage and recognition of the disease consequently more difficult, puncture of a gland might yield information of considerable value in arriving at a diagnosis.

In simple adenitis the picture is one of lymphoid hyperplasia, as is evidenced by the presence of large numbers of lymphoid cells in various stages of maturity, plus the presence of polymorphonuclear neutrophile leucocytes, the number depending upon the acuteness of the process. As has been mentioned, microorganisms responsible for the condition may also be seen occasionally.

In only one instance was a gland punctured which proved to be the site of a metastasis of a malignant tumor. Clinically, the case resembled Hodgkin's disease, but the blood picture was not that usually seen in any stage of Hodgkin's disease and the enlarged cervical glands, which had been treated by X-rays for a year, were very tender. The material obtained on puncture was very rich in cells the majority of which were of enormous size, some with one, others with several nuclei but practically all showing a vacuolated protoplasm. There were also multinucleated giant cells of a type quite different from "Dorothy Reed cells." Ordinary lymphoid cells were very scanty. Sections of an excised gland showed that all of the essential features of the picture had been observed in the puncture preparations. The diagnosis remains uncertain. Somewhat similar tumors have been seen arising from the nasopharynx and occasionally from the adrenal. From the sections it is evident that the gland is involved by a malignant tumor assumed to be metastatic, although the site of the primary growth has not been discovered. Following treatment with radium the glands have decreased markedly in size and the tenderness has practically disappeared.

Comment

The shortcomings of the method are as follows:

(1) From a fibrotic gland very little cellular material may be recovered, sometimes not enough to enable one to make a diagnosis.

(2) The cellular picture obtained is necessarily that from a very limited area of the gland, quite possibly not the area in which characteristic changes have occurred. A tuberculous gland, for instance, may show involvement in only one pole and none near the site of the puncture.

(3) The architecture of the gland is not shown as a rule, although occasionally a small bit of the gland is removed intact in the course of the puncture. The relation of the cellular elements to the reticulum, the amount of connective tissue reaction, the question of the invasiveness of the process present in the gland, are points on which information is rarely obtained from gland puncture.

Although these three points serve to limit the value of the method as a diagnostic aid it should be pointed out that in the great majority of glands which I have punctured (1) there has been no difficulty in securing adequate material for satisfactory preparations; (2) the disease process has not been localized but general throughout the gland; (3) the cellular picture has been sufficient to establish the diagnosis without a knowledge of the architecture of the gland. Whether the puncture has yielded the necessary information or not, the possibility still exists of excision of the gland for histological study and this procedure is to be recommended in all cases, at least until one has learned to interpret the results obtained by puncture. The appearance of cells stained with a Romanowsky stain and examined with an oil-immersion lens is so different from the appearance presented by cells of the same kind in an ordinary section stained with hæmatoxylin and eosin, that it requires some practice to build up a mental picture of the normal gland, to distinguish the normal from the abnormal elements and to recognize the types of pathological cells which are present.

Two other drawbacks might be mentioned as possibilities, (a) the spread of infection by puncture of infected glands—although this has not been observed in the patients with infected glands in this series—and (b) the dissemination of tumor cells when the process in the gland is malignant. I have punctured only one gland which was the site of a neoplasm and in that instance the patient had been regarded clinically as having Hodgkin's disease, as was mentioned above. Prompt radiation reduced the size of the glands and no ill effect from the puncture has been apparent. If the process in the gland were suspected of being malignant, one might well hesitate about undertaking a puncture, although in many instances it might establish the diagnosis without materially increasing the gravity of the outlook for the patient.

The advantages of the method may be set forth briefly:

(1) Rapidity; not infrequently a definite diagnosis may be made in 10 or 15 minutes.

(2) Thin preparations like blood films are secured, suitable for the application of a blood stain or special stains for cells, bacteria or protozoa and permitting the use of an oil-immersion lens in their study.

(3) The procedure is practically painless to the patient—more so than an ordinary venipuncture—and leaves no scar.

(4) It does not interfere with subsequent excision and histological study of the gland.

BIBLIOGRAPHY

1. Chatard, J. A., and Guthrie, C. G.: Human Trypanosomiasis, Report of a Case Observed in Baltimore, Am. Jour. Trop. Dis. and Prev. Med., 1914, I, 493.

2. Grieg, Capt. E. D. W., and Gray, Lieut. A. C. H.: Note on the Lymphatic Glands in Sleeping Sickness, Brit. Med. Jour., 1904, I, 1252; *also*, Lancet, 1904, I, 1570; *also*, Reports of the Sleeping Sickness Commission of the Royal Society, 1905, VI, 7.

3. Schaudinn, Fritz, and Hoffmann, Ehrich: Ueber Spirochætenbefunde im Lymphdrüsensaft Syphilitischer, Deut. med. Wchnschr., 1905, XXXI, 711.

3. Hoffman, Ehrich, and Beer, A: Weitere Mitteilungen über den Nachweis der Spirochæta pallida in Gewebe, Deut. med. Wchnschr., 1906, XXXII, 869.

3. Habermann, R., and Mauelshagen, F.: Die Bedeutung der Hoffmannschen Drüsenpunktion für die Früherkennung der Syphilis, Deut. med. Wchnschr., 1920, XLVI, 574.

3. Frühwald, Richard: Ueber Spirochätenbefunde in Lymphdrüsen, Wien. klin. Wchnschr., 1920, XXXIII, 999. (Good bibliography.)

3. Schultz, Edwin W.: A Method For Demonstrating Spirochæta Pallida in Regional Lymph Glands, Jour. Am. Med. Assn., 1920, LXXV, 176.

4. Stitt, E. R.: The Diagnostics and Treatment of Tropical Diseases, Ed. 3. Philadelphia, P. Blakiston's Son and Company, 1919, p. 164.

4. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, Ed. 3, New York, Wm. Wood and Company, 1920, p. 1429.

5. Manson, Sir Patrick, and Shipley, A. E.: Nemathelminthes, *in* Allbutt and Rolleston's A System of Medicine, London, Macmillan and Co., 1907, II, Part II, 942.

6. Meyer, K. F.: Afrikanisches Küstenfieber, *in* Kolle and Wassermann's Handbuch der Pathogenen Mikroorganismen, II, fl. Jena, Gustav Fischer, 1913, VII, 543.

7. Cochran, Samuel: Leishmaniasis in China, Jour. Am. Med. Assn., 1911, LVII, 1630.

8. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, Ed. 3, New York, Wm. Wood and Company, 1920, p. 1538 and p. 1653.

9. White, William Charles, and Pröscher, Frederick: Spirochætes in Acute Lymphatic Leukemia and in Chronic Benign Lymphomatosis (Hodgkin's Disease), Second Communication, Jour. Am. Med. Assn., 1907, XLIX, 1115; Experimental Lymphatic Spirillosis in Guinea-pigs, Jour. Am. Med. Assn., 1907, XLIX, 1908.

10. Personal communication from Dr. White.

THE PRESENT VIEWS ON ANAPHYLAXIS*

By JULES BORDET

Professor of Bacteriology, Parasitology, and Epidemiology, University of Brussels, Belgium; and Director of the Pasteur Institute, Brussels, Belgium.

The problems suggested by anaphylaxis are in reality manifold. They are at least three in number. First, we have to unravel the causes of the shock, to detect the factors to which the anaphylactic disturbances are due; this is a problem of etiology. Next, we have to discover which organs are primarily involved in the shock, and how the primary troubles can eventually bring about secondary disturbances; this is a question of symptomatology. The third problem has to do with general pathology; what is the rôle played by anaphylactic phenomena in the course, symptoms, or peculiarities, of several diseases, such as serum sickness, asthma, tuberculosis with its so much discussed hypersensitiveness toward tuberculin, intoxications with special reference to drug idiosyncrasy, and so on? There is no need to say that I cannot, in the brief space of time at my disposal, consider all of these problems; I intend to devote special attention only to the first of them, the predominant importance of which lies in the fact that it must necessarily be solved before any correct answer to the others can be arrived at. For example, the question as to the true anaphylactic nature of tuberculin hypersensitiveness cannot be decided until anaphylaxis itself has been suitably and strictly defined, such a definition of typical anaphylaxis depending upon a complete knowledge of its symptomatology and particularly of its cause. As a matter of fact, this essential point has not as yet been satisfactorily settled. Writers do not agree completely as to the extent and limits of the field of anaphylaxis. Some of them think that the term anaphylaxis ought to be retained to designate exclusively the phenomena depending upon the interaction of an antigen and an antibody. Others, myself included, strongly incline to the belief that the actual anaphylactic shock, with all of its characteristic symptoms, though resulting readily and frequently from such a cause, can also be brought about by quite different factors. However apt they may be to develop the shock, antigen-antibody complexes, nevertheless, in certain cases might be dispensed with. Were such an assumption true, the concept of anaphylaxis would expand in a much broader field, in which probably many morbid phenomena, occurring in the course of several diseases and apparently not dependent upon the activity of an antibody, could be included. Such being the case, the classification proposed by certain writers, which distinguishes completely, for instance, between allergy and

* Lecture II of the Herter Series, delivered before The Johns Hopkins University on Wednesday, October 27, 1920.

drug idiosyncrasy and real anaphylaxis, ought to be revised. Undoubtedly, anaphylaxis would include more numerous phenomena and consequently gain a much larger significance, were the intervention of an antibody, at least in certain cases, not necessary.

It follows from these considerations that, among all the problems connected with anaphylaxis, the one most important—since on its solution depends the very definition of anaphylaxis—is to determine the fundamental reaction giving rise to the typical disturbance. In reality, it appears as though many investigators had devoted themselves less to the understanding of this interaction in its intimate nature than to the determination of its localization. The point most vehemently in dispute at the present time is that of the site of the reaction which is the immediate causal factor of the shock. Two theories, the cellular and the humoral, are thus to be considered, but I am of opinion that they are not as irreconcilable as many investigators tend to believe. Both of these are certainly supported by indisputable evidence and consequently each seems perfectly justified in certain cases. Hence it is evidently necessary to bring them into harmony. However keen may be the interest in knowing where the primary reaction takes place, unquestionably the main thing is to ascertain of what this reaction consists; and it may be presumed that its intimate nature will be, for technical reasons, more easily and successfully investigated in a humoral medium than in a cellular protoplasm. I shall, therefore, try to show that all of the objections raised against the humoral theory are not equally convincing, and that the experiments planned in the direction of humoral analysis are particularly capable of suggesting correct and useful ideas.

In order to explain as clearly as possible the problem of anaphylaxis, it would probably be well to follow chronologically the successive discoveries as they have been linked one with another. But I shall not presume to review, in detail, ideas which you know as well as I do, and perhaps better. Indeed, among the countries which have supplied a large amount of information regarding anaphylaxis, America stands high. American writers, by their number as well as by the value of individual investigations, have taken a prominent part in, and greatly contributed to, the success of the study. Every one knows what we owe to the researches of Theobald Smith, Gay, Southard, Rosenau, Anderson, Frost, Lewis, Auer, Pearce, Eisenbery, Weil, Wells, Osborne, Coca, Schultz, Manwaring, Zinsser, and many others.

As you remember, the term "anaphylaxis" originated with Richet, and was intended to designate the strange fact that an organism subjected to a first injection may become highly susceptible to, instead of immune from, the action of certain poisons, such as the liquid extracted from the body of the mussel or from the tentacles of actinia. Far from protecting the animals, a first injection of such toxic matters rendered them, for a long period, hypersensitive to a subsequent injection. Although striking, this discovery acquired its whole value and significance only through the researches of Arthus, Rosenau and Anderson, who proved that non-toxic albuminoids could give rise to closely allied phenomena. As Arthus showed, horse serum causes no local nor general disturbance when injected subcutaneously into normal rabbits; but when injected into rabbits who have been previously submitted to injections of the same serum, the results are totally different; at the point of inoculation, œdema, induration and occasionally gangrene are observed. Furthermore, a rabbit previously and repeatedly injected may die very rapidly, showing convulsions, and extreme dyspnœa, when intravenously injected with a dose of horse serum harmless to normal animals. Rosenau and Anderson, and soon after, Otto, made a careful study of these phenomena, especially as they affect the guinea-pig. Theobald Smith had already shown that guinea-pigs, after having served as tests for anti-diphtheria serum, that is, having received a very small quantity of horse serum, showed themselves, nearly two weeks later, strangely susceptible to the injection of the same fluid. Rosenau and Anderson ascertained that the condition of hypersensitiveness appeared twelve or fifteen days after the first injection; and further, that minimal amounts, even traces of horse serum were sufficient to sensitize the animals. The second injection, or test injection, dangerous when made into the peritoneal cavity, was still more so when given intravenously; even one-tenth of a cubic centimeter of serum might kill the animal. These writers observed also that, after a female guinea-pig has been sensitized, its offspring is found to be in the same condition. The determination of the nature of the substances capable of inducing sensitiveness was soon completed. Foreign sera, milk, sperma, egg-white, microbes, albuminoids extracted from plants, in short, many proteins capable of functioning as antigenic substances, that is, of giving rise to antibodies, sensitize in very small doses, but lose this property if subjected to coagulating or disintegrating influences before being injected. Carbohydrates, fats, lipoids, do not sensitize; as is well known, they do not belong to the category of antigens.

It was thus readily conjectured that the appearance of sensitiveness must have a connection with the production of those antibodies which characterize immunity. This idea coincided with the important findings, first, that sensitizing substances are antigens; secondly, that sensitiveness does not appear until several days after the inducing injection. Moreover, the capacity of sensitizing, and that of killing at the time of the second injection, belong to one and the same substance. Thus, it may be assumed that the first injection produces antibodies, and that the conflict between these antibodies and the same reinjected antigen produces the disorders. It may thus be understood why anaphylaxis, like antibodies, is highly specific. As is well known, this view of the important rôle of antibodies in anaphylaxis received unquestionable confirmation when Nicolle, Gay and Southard, and Otto, discovered *passive anaphylaxis*, the serum of animals in a condition of sensitiveness injected into normal animals transmitting to them the same condition. Just as there exist two different aspects of immunity, similarly an active and a passive sensitiveness must be distinguished. A close parallelism exists between the sensitizing capacity of an immune serum and its

content of antibodies. A very small dose of the serum of highly immunized animals can confer the sensitiveness. Just as is observed in immunity, passive sensitiveness appears more rapidly than active sensitiveness. The nature of the antibody responsible for the production of sensitiveness varies, as may be expected, with the nature of the antigen under experiment. In the case of red corpuscles, the antibody concerned is the hæmolytic one; in the case of a foreign serum, milk or egg-white, it is in all probability the precipitin which, as a matter of fact, confers also the avidity toward alexin or complement. Treated *in vitro* with the corresponding antigen, an immune serum loses proportionally its power of inducing sensitiveness towards the same antigen. A quite analogous phenomenon may occur *in vivo;* in fact, the sensitiveness of an animal possessing a specific antibody may disappear through the neutralization of the latter when the corresponding antigen is injected, and this is an essential reason, if not the only one, for the condition known as anti-anaphylaxis. As is well known, a guinea-pig sensitized to a given antigen, and which, on being injected with an infralethal dose of the latter, suffers from the shock but recovers, will subsequently resist quantities of the same antigen much larger than the fatal dose. In such a case, anti-anaphylaxis appears as a veritable desensitization due to the neutralization of the antibody requisite for the shock. But, as we shall see further, still other factors may have as an effect the conferring of a condition of anti-anaphylaxis; the susceptibility to the shock itself may decrease.

To sum up, in all of the investigated cases of anaphylaxis depending on the intervention of an antigen, the interaction antigen-antibody represents the primary cause of the accidents. This notion, of course, does not include the hypothesis—which we shall find to be not groundless—that some substances may be capable of developing the shock in spite of their not belonging to the category of antigens or antibodies.

What are the symptoms of anaphylaxis? On this point, we are indebted to American scientists for the greater part of the information collected. We owe to Rosenau and Anderson a careful study of the shock. This was soon followed by the contributions of Gay and Southard dealing especially with the post-mortem condition and by the very accurate study of Auer and Lewis. As you know, when a sensitized guinea-pig receives the test injection, within one or two minutes it begins to be excited, scratches itself, jumps convulsively, coughs, then staggers and finally falls over, showing extreme dyspnœa; the symptoms are those of asphyxia. At the autopsy, a dominant pathological finding is the inflated condition of the lungs, due, as Auer and Lewis have shown, to a contraction, peripheral in origin, of the smooth musculature of the bronchioles, the effect of which is that air can be admitted into the chest by violent inspiratory efforts, but can not be expelled. The liver is much congested and swollen. This symptom is particularly evident in dogs, as Manwaring has pointed out. There is also a surprising persistence of the heart beat, especially of the auricles. In many cases, there are small hemorrhages, scattered in the lungs and other tissues, due in all probability, according to Gay and Southard, to lesions of the endothelium.

Other important symptoms of the shock consist in a fall of blood pressure and temperature, a lowering of blood coagulability and of the number of circulating leucocytes and platelets. That the smooth musculature is affected in the shock is proved beyond any doubt by the remarkable researches of Schultz and of Dale, which showed that fragments of small intestine or uterus from sensitized guinea-pigs, immersed in Ringer's solution, contract when there is added to this bath some of the antigen towards which the animal has been sensitized. This experiment undoubtedly explains the fatal bronchiole muscle contraction causing asphyxia. Dale has found recently that if the lungs of an anaphylactic guinea-pig are removed from the body and perfused clear of blood with Ringer's saline solution, addition of a trace of the specific antigen to the perfused fluid causes an immediate contraction of the bronchioles, so intense that air cannot be forced through them. The effect, like the sensitiveness itself, is perfectly specific.

The part played by the smooth musculature in the shock is evident, but, as has been already said, other cells also appear to be affected, especially the endothelial cells, and perhaps also the heart tissue. Since several tissues are involved in the shock, it is easily conceivable that the immediate cause of death may vary with the nature of the tissue most injured, and consequently that the symptoms elicited in different animal species may be not altogether identical. In general the anaphylactic process is the same, but different aspects may be assumed. Smooth musculature is gravely affected both in the guinea-pig and the rabbit, but in the guinea-pig the muscles most markedly implicated are those of the bronchioles, whereas in the rabbit one observes particularly, according to Coca, constriction in the muscular coat of the pulmonary arterioles, the effect of which is to bring about an obstruction to the pulmonary circulation. In dogs, as Manwaring has pointed out, the liver plays a very important part in the shock; the greater portion of the blood is suddenly accumulated in this organ as an effect of an influence exerted on the endothelial cells of its capillaries.

However, these are simply differences in the order of susceptibility of the different tissues concerned in the shock, and thus the discrepancies in detail revealed by the different animal species need not deter us from the opinion that, in the main, the anaphylactic process is everywhere the same as regards its fundamental character. As a matter of fact, the symptoms of shock, though always analogous, are not absolutely identical even in one and the same species, whatever antigen be used. This point has, perhaps, received too little attention. For instance, guinea-pigs sensitized towards horse serum or foreign corpuscles do not, when succumbing to the effects of the injection of the corresponding antigen, show exactly the same lesions. Thus, the tendency to pulmonary hæmorrhages is ordinarily much more marked in the guinea-pig which receives foreign blood corpuscles; sometimes, just before death, a bloody serum or even drops of blood flow from the nostrils. Probably the anaphylactic poison, although resulting in all cases from a similar reaction, is not always

exactly the same, the adsorption properties of the different antigens being not absolutely identical. It being thus established that certain cells are particularly involved and that the shock is due to an antigen-antibody interaction, the question immediately arises as to the primary site of this interaction. Does the latter occur in the sensitive cells themselves, or does it take place in the circulating humors, producing in them some toxic substance capable of reaching subsequently the cells and injuring them? We now approach one of the most disputed points. The cellular theory has found its supporters especially in America and in England, chief among them being Richard Weil, Coca, and Dale. You will recall their main arguments. A very striking one consists in the fact that, at least in the guinea-pig and in the case of many antigens, passive hypersensitiveness is not communicated at once by the injection of the sensitizing serum, as ought to be expected from analogy with passive immunity. For example, susceptibility to horse serum in the guinea-pig appears only some hours after the intravenous injection of the immune serum active towards this antigen, and much later when the same serum is injected subcutaneously. In order to explain this singular fact, first observed by Rosenau and Anderson, Gay and Southard, Doerr and Russ advanced the hypothesis that the antigen-antibody reaction has dangerous consequences only when it takes place in the tissue cells themselves. As a matter of fact, this condition seems to be easily fulfilled because, as was shown by Fenyvessy and Freund, Manwaring, Coca, Weil and others, a large amount of the antibody injected into the circulation rapidly disappears from the blood, being in all probability anchored by the cells. Weil thinks that sensitiveness is caused exclusively through the agency of the absorbed antibody, and that circulating antibodies, on the contrary, exert a protective influence by uniting with the antigen before the latter can reach the cells. To sum up, the interaction, dangerous when it occurs in the cells, is innocuous when it takes place in the blood. The researches of Schultz and Dale, showing that smooth musculature even when freed from its blood is susceptible to the antigen, distinctly support this notion. Nevertheless, I am of opinion that, however correct this view may be in many cases, it cannot be generalized, and that it would be entirely unjustifiable to deduce from it that all of the experimental results dealing with the production *in vitro* of anaphylatoxins ought to be wholly disregarded, as being in contradiction to the cellular theory of anaphylaxis. Such an undue generalization of this assumption that the shock depends upon the occurrence of the antigen-antibody interaction in the cells of vital organs, no disturbance being caused by interaction with a circulating antibody, is to be found, for example, in a paper recently published by Dale, who notes that the subcutaneous injection of the antigen with or soon after the antibody, is uniformly without effect, at any rate in guinea-pigs, and that, as a rule, attempts to produce *in vitro* a real anaphylatoxin through the interaction of antigen and antibody, have failed.

Aside from the fact that in the dog and in the rabbit the sensitizing serum confers sensitiveness without any delay, it may be argued, as regards the guinea-pig, that Dale takes no account of the fundamental experiment showing that passive anaphylaxis towards red corpuscles establishes itself at once. A guinea-pig intravenously injected with rabbit's red corpuscles succumbs to the shock if the corresponding guinea-pig immune serum has been injected into the vein immediately before, or even if it is administered soon afterwards. A similar result is observed when a guinea-pig receives corpuscles which have been treated *in vitro* by the heated corresponding immune serum, and have thus absorbed the specific antibody. Evidently, under such circumstances, the blood plasma instead of the cell protoplasm, is involved in the conflict with the complex antigen-antibody already developed. Furthermore, such rabbit's corpuscles treated with the specific antibody produce *in vitro* a very active anaphylatoxin, when added to fresh normal guinea-pig serum. Hæmolysis having occurred, the mixture is freed from the corpuscle's stromata by centrifuging and pipetted off; this clear fluid produces a typical shock. It cannot be doubted that the symptoms due to the injection of the corpuscle-antibody complex are of the true anaphylactic nature; the circumstances under which they are elicited are wholly in harmony with the definition of anaphylaxis. Now, since the anaphylatoxin produced *in vitro* by mixing such corpuscles with fresh serum brings about exactly the same shock, its connection with typical anaphylaxis is obvious and its significance cannot be questioned.

I know the objection has been raised that the toxic fluid alluded to contained free hæmoglobin and that substances liberated by injured cells may give rise to disturbances having nothing to do with anaphylaxis. But the objection is untenable, since no poison is generated, in the absence of the antibody, when normal guinea-pig serum is added to corpuscles which have been hæmolyzed by distilled water or freezing. It is quite certain that the cellular theory of anaphylaxis cannot be applied to the case of red corpuscles serving as antigen.

Consequently, as regards the primary site of the anaphylactic reaction, neither the humoral nor the cellular theory can be exclusively accepted. Each of them may be true, and it depends upon the antigen. Sometimes the perturbing substance which represents the immediate cause of the shock is engendered in the blood, sometimes it can appear only in the cellular protoplasm, the previous fixation of the antibody by the cells being in such cases a necessary condition.

Is it conceivable that the nature of the various antigen-antibody complexes is so different that they are capable of producing the poison sometimes in the blood, sometimes only in the cells? The discrepancy can be explained if one supposes that the complexes are involved in an adsorption phenomenon occurring between them and some constituents of the medium, the composition of the latter being thus disturbed. It is a recognized fact that adsorption phenomena are easily influenced, that they depend, for instance, on the alkaline or acid reaction, the action of salts, the nature of the colloidal substances present; and it has likewise been proved that different substances capable of adsorption are not necessarily influenced in the same manner or to the same extent by a given

factor. Next, it may be presumed that, as complexes containing different antigens do not possess, in all probability, quite identical absorbing properties, such properties will require, to be clearly manifested, special conditions not likely to be the same for all of the complexes; in other words, a given complex will adsorb best in a given medium, some complexes operating better in a cellular, others in a humoral one. To sum up, the question as to the primary site of the interaction does not appear to have such fundamental importance as has been asserted. Whatever may be the site, the chief problem is to elucidate the nature of the interaction. In all probability, the underlying mechanism of the shock consists in the production of a toxic principle, derived, under the influence of the antigen-antibody complex, from the constituents of the surrounding medium, humoral or cellular, a principle to the presence of which the typical disturbances of the sensitive cells are due.

Were the significance of the anaphylatoxins prepared *in vitro* accepted by the adherents of the cellular hypothesis, the views just expressed could serve as a connecting link between the two otherwise conflicting theories. But such is not the case. According to many writers, the anaphylatoxins, being produced *in vitro* through the agency, not of cells, but of serum, cannot represent the real factor of anaphylaxis. No theoretical reasoning, however, can prevail against an experimental fact, and, as I reminded you before, the mixture of fresh guinea-pig serum and red corpuscles loaded with the specific antibody represents a true anaphylactic poison. Moreover, with this unquestionable anaphylatoxin is connected the one obtained by Friedberger in treating specific precipitates with fresh serum. Considering not alone the similarity of the symptoms elicited, but also the striking analogy between the methods of preparation, taking into account, for example, that in both cases the serum used to produce the poison must be fresh and is rendered inactive when heated to 55° C., one cannot refrain from concluding that the important facts discovered by the supporters of the cellular theory must be brought into harmony with the belief in the unquestionable significance of the several anaphylatoxins which have been described. Whatever may be the site, intracellular or intravascular, of its production, the poison called anaphylatoxin is the causal agent of the shock, the etiological problem resolving itself into that of the genesis of the anaphylatoxin, or, of the anaphylatoxins, the plural allowing the hypothesis that the poison may vary to a certain extent when the antigens are different.

What is the origin of the anaphylactic poison? As is well known, its appearance has been ascribed to the action of proteolytic ferments which might liberate toxic products at the expense of albuminous matters. This conception has been supported chiefly by Vaughan and Wheeler. Wells, Biedl and Kraus pointed out the real analogy existing between the symptoms of anaphylaxis and the effects of the injection of peptone. Assuming likewise that a digestion of the antigen furnished the poison, Friedberger thought that the proteolytic influence was exerted by the alexin or complement with the coöperation of the previously absorbed specific antibody. All of these conceptions, based on the hypothesis that the poison is materially derived from the antigen, are liable to serious objections. The presence of proteolytic ferments in the blood after the first injection of an antigen is not concomitant with the condition of sensitiveness. There exists not the least proof of an enzymatic property on the part of alexin or complement. The phenomena due to the lytic influence of alexin, as bacteriolysis and hæmolysis, are not accompanied by modifications indicating any chemical decomposition of albuminoids.

The foregoing theories being inadequate, it might be surmised that the toxic substance, instead of being derived from the antigen, is evolved from the serum, or from the cellular protoplasm, with which the antigen-antibody complexes are brought into contact, these media being modified in their constitution as a consequence of the adsorbing properties of the complexes. This idea originated with researches which, in conjunction with Gengou, I reported nine years ago. We described a peculiar phenomenon called by us the coagglutination of red corpuscles. We were able to show that the complexes antigen-antibody may possess very strong adsorption properties which are capable of being displayed even toward cells. We, therefore, suggested the hypothesis that perhaps the appearance of toxicity in a serum treated by such a complex might result from an adsorption phenomenon. The composition of blood plasma is very complex and still but little known. The number of active substances contained in it, taking part in the regular working of physiological functions, is undoubtedly considerable. All of them are necessary to the physiological equilibrium, and it may thus be presumed that the removal of certain of these principles may communicate abnormal properties to the plasma and even render it dangerous. This view was soon upheld by several writers, especially Doerr and Ritz, and some attempts were made to produce a toxin by adding to fresh serum certain adsorbing substances, such as kaolin. But the results were inconstant, and not convincing. The correctness of the idea was finally proven in 1913, when I discovered that ordinary agar is a very suitable and efficient adsorbent. I saw that fresh guinea-pig serum, when incubated even with traces of an emulsion of agar, is converted into a powerful anaphylatoxin. For example, twenty-five or fifty centigrams of agar, dissolved by heating in one hundred cubic centimeters of physiological salt solution, give when cool a flaccid mass which is easily transformed by shaking into a viscous fluid, to which five parts of fresh serum are added. Incubated for about two hours, the mixture is centrifugalized; the agar is wholly deposited, the clear supernatant fluid pipetted off and injected in a dose of from 3 to 5 c. c. into the jugular vein of a guinea-pig, kills it in a few minutes, the symptoms exhibited being precisely identical with those of anaphylactic shock. Excitement, jumping, cough, convulsions, symptoms of asphyxia, inflation of the lungs, ecchymosis, long duration of heart pulsation, very slow or no coagulation of the blood—nothing is missing. Of course, normal serum, not treated with agar and injected in the same dose, produces no appreciable effect. The agar-anaphylatoxin resembles closely the anaphylatoxin obtained by Friedeman or

Friedberger by contact of serum with antigens in the presence of the antibodies. No toxin is obtained when agar is mixed, not with fresh serum, but with serum previously heated to 55° C. Friedberger has likewise pointed out that heated serum is not suitable for obtaining his anaphylatoxin. But if anaphylatoxin be prepared by means of unheated serum and agar, it does not lose its toxicity when heated to 55-60° C., and the same fact may be observed with regard to the anaphylatoxin obtained, for example, by contact of fresh serum and foreign red corpuscles loaded with the specific antibody. The fact that anaphylatoxin resists such temperature excludes the possible objection that the coagulating principle of the serum, fibrin-ferment or thrombin, may be responsible for the toxic effects, since it is destroyed much more easily. The activity of thrombin decreases so rapidly, that normal serum is toxic for only a very short period after its production. On the contrary, when kept at the room temperature, the agar anaphylatoxin is still toxic after several months. Calcium salts are not requisite for the production of the poison, the latter appearing as well in the presence of sodium oxalate. Saturation with carbonic oxide gas favors the production of the poison.

My observations on agar-anaphylatoxin have been confirmed by Nathan, Loewit and Baeyer, Ropaczewski and Muttermilch, and in this country by the remarkable researches of Novy and de Kruif. Nathan even found that agar could be replaced by starch, although the effect is not so striking. Ropaczewski asserted that sodium pectate had the same property. Zunz and Gelat observed that horse serum could also be rendered toxic by agar. Novy and de Kruif found that rat serum was still more suitable than guinea-pig serum.

Soon after I had made known the agar-anaphylatoxin, Friedberger tried to reconcile this discovery with his own theory by assuming that agar contained some albuminous matter which was digested under the influence of alexin and thus liberated toxic products. But at the International Medical Congress held in London in 1913, I was able to refute that objection by demonstrating that starch entirely loses its property of inducing the formation of anaphylatoxin when liquified by the saccharifying diastase, which of course does not act on albuminous matters, and, consequently, the toxigenic property of starch is not due to such substances. Furthermore, I was able, in coöperation with Dr. Zunz, to obtain a purified agar containing no trace of nitrogen but which still induced the formation of an anaphylatoxin. Similarly, Ropaczewski asserts that the pectate which gave positive results was quite free from nitrogen.

Not every colloid or suspension of the particles is capable of converting the serum into anaphylatoxin. As Nathan showed, a suspension, not a solution of inulin, is apt to act as agar does, but I did not succeed when I tried gelatinous silicic acid, animal charcoal, gum arabic or some gelatinous precipitates such as tricalcic phosphate; moreover, the results obtained by some writers with kaolin have been disputed.

Such being the facts, the conclusion I felt entitled to state, and against which I think nothing could be objected, was, that the capacity of agar to convert, by a simple phenomenon of adsorption, the fresh serum into anaphylatoxin, demonstrates that the poison does not proceed from any digested antigen, but is derived from the normal constituents of the organism itself and that the frequent appearance of anaphylatoxin in the course of immunity phenomena arises simply from the fact that the complex antigen-antibody is endowed with adsorption properties quite analogous to those so distinctly displayed by agar.

Is anaphylaxis, then, the reverse of immunity? Evidently not. It is a secondary phenomenon, certainly harmful, but which, far from betraying an excessive and unwonted receptivity, testifies on the contrary that the factors of immunity are operating. In short, it is an accident in the course of the defence.

Unhappily, although those results are already seven years old (if the period of war, so unfavorable to scientific work, is to be taken into account), the intimate nature of the reaction occurring between agar and serum is still very mysterious. Agar has been supposed to remove an antitryptic agent and thus allow a desintegration of the albuminous constituents of the serum, but the attempts of Zunz and myself, and of Novy and de Kruif to test this hypothesis by detecting an increase of amino-acids in the agar anaphylatoxin did not favor this assumption. Novy and de Kruif think that the evanescent toxicity of blood just before or soon after spontaneous coagulation is to be attributed to a principle similar to the anaphylatoxin. I do not believe this opinion to be correct. The toxicity of clotting blood or of quite fresh serum is sufficiently explained by the presence of thrombin, the coagulating activity of which decreases, just as does its toxicity, very rapidly. True anaphylatoxins are stable. The same toxicity of recently clotted blood may appear in any serum, at any moment, provided it contains a sufficient amount of serozym, simply by adding, in the presence of calcium, platelets or cytozym to it, fresh thrombin being thus produced. But cytozym and calcium salts are not, so far as I could ascertain, necessary to the production of anaphylatoxin. In short, the conversion of serum into a toxin by the mere influence of agar has not been explained.

I think that sufficient evidence has been afforded by the foregoing considerations in favor of the view that the conception of anaphylatoxin, even when the poison is obtained through the agency of a non-antigenic substance such as agar, contributes very much to the understanding of the shock occurring in animals actively or passively sensitized towards an antigen. The connection between the different facts appears to be satisfactorily established. But it seemed desirable to make it still more evident. Perhaps this need has been met, to a certain extent at least, by researches carried on by me during the war concerning antianaphylaxis. I found that agar anaphylatoxin may be produced, not alone *in vitro*, but also *in vivo*, simply by injecting intravenously into a guinea-pig a small amount of agar emulsion. Under such conditions, the interaction giving rise to the poison occurs in the circulation itself. The same fact was observed, independently, of

course (no communication being then possible between invaded Belgium and civilized countries), by the American scientists, Novy and de Kruif, and also by Zunz. But I observed further that when a guinea-pig is given, intravenously, agar in somewhat less than the lethal dose, it becomes capable, after its recovery from the shock, of resisting a quantity of agar at least sufficient to kill an unprepared guinea-pig. This is undoubtedly an example of antianaphylaxis, but one which of course could not be interpreted by the neutralization of an antibody, since no antibody is in question in the case of agar. Now, it must be noticed that, even in the case of anaphylaxis due to the intervention of antigen and antibodies, the condition of enhanced resistance or antianaphylaxis is not entirely explained by the assumption, mentioned above, that the antibody has been neutralized by the injected antigen. The latter influence certainly plays an important rôle, but it must be pointed out that, aside from this protecting factor, the animal becomes more able to withstand the shock itself. This may be proved by experimenting, for example, with red corpuscles which have absorbed the specific antibody. An infralethal dose injected intravenously develops a curable shock. Then, after recovery, the animal is more able than before to withstand the lethal dose. In such a case the acquired tolerance clearly results from a physiological response to the poisonous action of anaphylatoxin produced *in vivo*. It could not be alleged that the animal resists better the second injection because the requisite antibody has been previously neutralized; in fact, antibody is never lacking, since it is introduced, together with the red corpuscles, by the second injection as well as by the first.

Now, how is this new aspect assumed by antianaphylaxis to be interpreted? I observed the following fact: Large guinea-pigs receive in the jugular an injection of half a cubic centimeter of agar-suspension at 0.25 per cent, a dose of a little less than the lethal one. They recover and are thereby enabled to resist, on the following day, the injection of one cubic centimeter of the same suspension, that is, of at least the lethal dose. Several hours later they are bled, and their serum is subsequently tested for its ability to be converted into anaphylatoxin, by the addition of agar in the ordinary amount of five parts of serum for one part of agar. Mixtures similar to these but containing serum of normal unprepared guinea-pigs are then employed. The result is, that the serum derived from the guinea-pigs treated with intravascular injections of agar has lost almost completely the capacity of producing *in vitro* anaphylatoxin under the influence of agar, whereas normal serum, as we know, is regularly endowed with this property. It is a quite remarkable fact that the same serum of prepared guinea-pigs gives, when treated with rabbit's red corpuscles loaded with the specific antibody, the same negative result; the liquid does not become toxic. Thus a very close connection is established between the different anaphylatoxins, prepared either with or without the interference of an antigen-antibody complex, and thus the experiments concerning agar gain a wider significance for the understanding of anaphylaxis as observed under ordinary circumstances. I may add that, similarly, the serum of guinea-pigs which have recovered from an injection of foreign red corpuscles loaded with antibody is markedly less capable than normal serum of giving anaphylatoxin when brought into contact with the same complex antibody-corpuscles. We consequently reach the conclusion that antianaphylaxis is due, at least partly, to a modification of the serum, consisting probably in the presence of some substance capable of protecting from the immediate factor of the shock, that is, from the anaphylatoxin.

It would be very interesting to investigate whether any interaction can be detected between the anaphylatoxin and the tissues, such as smooth musculature, which are particularly susceptible to the shock. We are working in Brussels on these lines, but such experiments are difficult owing to the fact that the tissue extracts are, as we know, poisonous in themselves. Perhaps some results will nevertheless be attained, but we must not anticipate. My only desire to-day has been to point out that it would be quite unjustifiable, however correct may be many assumptions of the cellular theory, to disregard the humoral side of the anaphylactic phenomena, and I feel particularly glad that several American writers, among them Novy and de Kruif, have successfully contributed to the discoveries in that direction. Anaphylatoxin has undoubtedly much to do with real anaphylaxis and even did such a connection not exist in reality, the capacity of normal serum to be converted readily into a poison by the action of agar is an unexpected and very striking fact, enigmatic enough to deserve, at any rate, the serious attention of the physiologist.

JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXII is in progress. The subscription price is $4.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, $5.00 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

NEW PUBLICATIONS.

The following monograph is for sale by The Johns Hopkins Press, Baltimore, Md.:

Relation of Tonsillar and Nasopharyngeal Infections to General and Systemic Disorders. By S. J. CROWE, S. SHELTON WATKINS and ALMA S. ROTHHOLTZ. 63 pages. Price, $1.25.

NOTES ON NEW BOOKS

The Oxford Medicine. By Various Authors. Edited by HENRY A. CHRISTIAN, M. D., and SIR JAMES MACKENZIE, M. D. Vols. I and II. (*London and New York: Oxford University Press, 1920.*)

It is with unusual interest that one approaches the volumes of the new Oxford Medicine. Appearing as they do at the height of an era of new ideas in medical thought, and sponsored by prominent and popular editors, one can be sure that they will contain much of interest and value. However, before attempting any review of this work one is tempted to collect his thoughts as to the ideal system or compendium of internal medicine. What should be its form, content, and purpose? One likes to think of it as a grand collection of information about disease, a storehouse of knowledge into which one may delve with the reasonable certainty of finding information which will clear up a doubtful point. It, therefore, is interesting to find that the Oxford system is planned along other lines—it is reflective rather than statistical, autobiographical rather than objective, and in general it tends more to bring out the point of view of an individual in regard to certain phases of medicine than to present an impartial résumé of what has been established as fact. Under these circumstances one discovers naturally an uneven quality in the various articles. Most of them are good, some are superlative, while a few are distinctly inferior.

Volume I contains a series of interesting articles on the general subjects of diagnosis and the relations of the fundamental sciences—biology and chemistry—to clinical medicine. The reflections of Christian and Mackenzie on the present and future of medicine form a pleasant introduction to the succeeding sections. The summary of protein chemistry in relation to disease by Van Slyke, acidosis by Henderson, and respiration by Peabody are perhaps the outstanding articles in this volume. The sections dealing with infection are less pleasing. The one on focal infection is especially replete with statements which surely cannot be acceptable to many physicians. Our own reaction is decidedly against the elevation of the doctrine of so-called focal infection to the dignity of a cult. It seems unnecessary to confuse the well established principles of sepsis by assumptions which, at best, are dubious.

Volume II, dealing with diseases of the lungs, heart and blood, contains many excellent articles. Those on leukæmia and on the diseases of the lungs stand out on account of their clearness and precision. One is surprised at the special article on massive collapse of the lung, a condition quite outside our own experience as a distinct disease entity. One may also criticize the article on asthma, in so far as it presents the subject from a narrow point of view only—that of anaphylaxis.

On the whole, the impression gained from the first two volumes of the Oxford Medicine is pleasant. As a summary of prevailing views in medicine it is of value, though one can in no sense think of it as a monumental work.

A. L. B.

PUBLICATIONS

The following twelve monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, $2.00.

The Operative Story of Goitre. The Author's Operation. By WILLIAM S. HALSTED, M. D. Price, $3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By CURLE L. CALLANDER, M. D. Price, $2.50.

Ligations of the Left Subclavian Artery in its First Portion. By WILLIAM S. HALSTED. Price, $2.00.

The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18. By WILLIAM G. MACCALLUM. Price, $1.50.

Pathological Anatomy of Pneumonia Associated with Influenza. By WILLIAM G. MACCALLUM. Price, $1.50. (This monograph will be on sale within a short time.)

are now on sale by THE JOHN'S HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $4.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.